EU Clinical Trials Register

Clinical trial results:
A Phase 3, Multi-Center, Open-Label Study to Investigate Safety, Efficacy, and Tolerability of Sildenafil Citrate in Pediatric Patients With Pulmonary Arterial Hypertension

Summary

EudraCT number	2016-003978-41
Trial protocol	Outside EU/EEA
Global end of trial date	

Results information

Result version number	v2
This version publication date	17 March 2017
First version publication date	24 November 2016
Version creation reason	• Correction of full data set Update to indicate Yes for Article 46 and that the study remains ONGOING.

Trial information

Trial identification

Sponsor protocol code	A1481298

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01642407
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer, Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, 110017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 18007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 18007181021, ClinicalTrials.gov_Inquiries@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	Interim
Date of interim/final analysis	20 May 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 May 2016
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate changes of patient status with Sildenafil treatment for individual Japanese pediatric patients with Pulmonary artery hypertension (PAH).

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Council for 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	24 August 2012
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: 6
Worldwide total number of subjects	6
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)	2
Children (2-11 years)	3
Adolescents (12-17 years)	1
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Study was conducted at 11 sites in japan.

Period 1

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

Arms

Arm title	Sildenafil

Arm description:

Subjects received 10 milligram (mg) or 20 mg of Sildenafil (based on their body weight) orally, thrice daily on Day 1 (Baseline), Week 4, 8 and 16. Subjects with less than or equal to (<=) 20 kilogram (kg) of body weight received 10 mg dose, thrice daily as powder for oral suspension and subjects with greater than (>) 20 kg of body weight received 20 mg dose, thrice daily as film-coated tablets.

Arm type	Experimental
Investigational medicinal product name	Sildenafil 20 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received sildenafil 20 mg tablet orally thrice on Day 1, Week 4, 8 and 16

Investigational medicinal product name	Sildenafil 10 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Subjects received sildenafil 10 mg per milliliter oral suspension orally thrice on Day 1, Week 4, 8 and 16

Number of subjects in period 1	Sildenafil
Started	6
Completed	4
Not completed	2
Insufficient clinical response	2

Baseline characteristics

Reporting groups

Reporting group title	Sildenafil

Reporting group description:

Subjects received 10 milligram (mg) or 20 mg of Sildenafil (based on their body weight) orally, thrice daily on Day 1 (Baseline), Week 4, 8 and 16. Subjects with less than or equal to (<=) 20 kilogram (kg) of body weight received 10 mg dose, thrice daily as powder for oral suspension and subjects with greater than (>) 20 kg of body weight received 20 mg dose, thrice daily as film-coated tablets.

Reporting group values	Sildenafil	Total	
Number of subjects	6	6	
Age Categorical			
Units: Subjects			
<=18 years	6	6	
Between 18 and 65 years	0	0	
>=65 years	0	0	
Age Continuous			
Units: years			
arithmetic mean	6.7		
standard deviation	± 5.4	-	
Gender, Male/Female			
Units: Subjects			
FEMALE	3	3	
MALE	3	3	

End points

End points reporting groups

Reporting group title	Sildenafil

Reporting group description:

Subjects received 10 milligram (mg) or 20 mg of Sildenafil (based on their body weight) orally, thrice daily on Day 1 (Baseline), Week 4, 8 and 16. Subjects with less than or equal to (<=) 20 kilogram (kg) of body weight received 10 mg dose, thrice daily as powder for oral suspension and subjects with greater than (>) 20 kg of body weight received 20 mg dose, thrice daily as film-coated tablets.

Primary: Change from Baseline in Pulmonary Vascular Resistance Index (PVRI) at Week 16

End point title	Change from Baseline in Pulmonary Vascular Resistance Index (PVRI) at Week 16[1]

End point description:

PVRI equals pulmonary vascular resistance (PVR) times body surface area (BSA) (PVRI = PVR*BSA). PVR is the resistance to blood flow through the pulmonary circulation and it was measured in Wood units. Wood unit =80 dyne*seconds per centimetre^5 (dyne*sec/cm^5).
Efficacy analysis set included all subjects who received at least 1 dose of study drug. Here, 'n' signifies those subjects who were evaluable at specified time points.

End point type	Primary

End point timeframe:

Baseline, Week 16

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 analysed for this primary endpoint.

End point values	Sildenafil			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: Wood units*meter^2				
arithmetic mean (standard deviation)				
Baseline (n =6)	18.567 (± 11.7629)			
Change at Week 16 (n =4)	-4.113 (± 6.377)			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Mean Pulmonary Artery Pressure (mPAP) at Week 16

End point title	Change From Baseline in Mean Pulmonary Artery Pressure (mPAP) at Week 16[2]

End point description:

It was a hemodynamic parameter and measured using a pressure transducer positioned at the mid-axillary line with the subject in the supine position.

Efficacy analysis set included all subjects who received at least 1 dose of study drug. Here, 'n' signifies those subjects who were evaluable at specified time points.

End point type	Primary

End point timeframe:
Baseline, Week 16

Notes:

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

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

End point values	Sildenafil			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: millimeters of mercury (mmHg)				
arithmetic mean (standard deviation)				
Baseline (n =6)	58.5 (± 22.94)			
Change at Week 16 (n =4)	-6.5 (± 15.15)			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in World Health Organization (WHO) Functional Class in Subjects With Pulmonary Arterial Hypertension (PAH) at Week 4

End point title	Change From Baseline in World Health Organization (WHO) Functional Class in Subjects With Pulmonary Arterial Hypertension (PAH) at Week 4[3]

End point description:

WHO functional classification for PAH range from Class I (no limitation in physical activity, no dyspnea with normal activity), Class II (slight limitation of physical activity), Class III (marked limitation of physical activity) and Class IV (cannot perform a physical activity without any symptoms, dyspnea at rest). The change from baseline in WHO functional class was classified into "Improved", "No change" and "Worsened". Improvement = reduction in functional class, worsened = increase in functional class and no change = no change in functional class. Change from baseline in number of subjects in each functional class were reported. Efficacy analysis set included all subjects who received at least 1 dose of study drug.

End point type	Primary

End point timeframe:
Baseline, Week 4

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 analysed for this primary endpoint.

End point values	Sildenafil			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: subjects				
Baseline: Class I	2			
Baseline: Class II	3			
Baseline: Class III	1			
Baseline: Class IV	0			

Week 4: Improved	1				
Week 4: No change	5				
Week 4: Worsened	0				

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in World Health Organization (WHO) Functional Class in Subjects With Pulmonary Arterial Hypertension (PAH) at Week 8

End point title	Change From Baseline in World Health Organization (WHO) Functional Class in Subjects With Pulmonary Arterial Hypertension (PAH) at Week 8[4]

End point description:

WHO functional classification for PAH range from Class I (no limitation in physical activity, no dyspnea with normal activity), Class II (slight limitation of physical activity), Class III (marked limitation of physical activity) and Class IV (cannot perform a physical activity without any symptoms, dyspnea at rest). The change from baseline in WHO functional class was classified into "Improved", "No change" and "Worsened". Improvement = reduction in functional class, worsened = increase in functional class and no change = no change in functional class. Change from baseline in number of subjects in each functional class were reported. Efficacy analysis set included all subjects who received at least 1 dose of study drug. Here,'N' signifies those subjects who were evaluable for this measure.

End point type	Primary

End point timeframe:

Baseline, Week 8

Notes:

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

End point values	Sildenafil			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: subjects				
Improved	1			
No change	4			
Worsened	0			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in World Health Organization (WHO) Functional Class in Subjects With Pulmonary Arterial Hypertension (PAH) at Week 16

End point title	Change From Baseline in World Health Organization (WHO) Functional Class in Subjects With Pulmonary Arterial Hypertension (PAH) at Week 16[5]

End point description:

WHO functional classification for PAH range from Class I (no limitation in physical activity, no dyspnea with normal activity), Class II (slight limitation of physical activity), Class III (marked limitation of

physical activity) and Class IV (cannot perform a physical activity without any symptoms, dyspnea at rest). The change from baseline in WHO functional class was classified into "Improved", "No change" and "Worsened". Improvement = reduction in functional class, worsened = increase in functional class and no change = no change in functional class. Change from baseline in number of subjects in each functional class were reported. Efficacy analysis set included all subjects who received at least 1 dose of study drug. Here,'N' subjects those subjects who were evaluable for this measure.

End point type	Primary

End point timeframe:
Baseline, Week 16

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 analysed for this primary endpoint.

End point values	Sildenafil			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: subjects				
Improved	1			
No change	3			
Worsened	0			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Brain Natriuretic Peptide (BNP) at Week 16

End point title	Change From Baseline in Brain Natriuretic Peptide (BNP) at Week 16[6]

End point description:

BNP is produced by ventricular cardiomyocytes. It causes reduction in preload and blood pressure by vasodilatation. Efficacy analysis set included all subjects
who received at least 1 dose of study drug. Here, 'n' signifies those subjects who
were evaluable at specified time points.

End point type	Primary

End point timeframe:
Baseline, Week 16

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

End point values	Sildenafil			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: picogram per milliliter				
arithmetic mean (standard deviation)				
Baseline (n =6)	132.62 (± 135.08)			
Change at Week 16 (n =4)	-64.1 (± 129.638)			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in N-terminal Pro Brain Natriuretic Peptide (NT pro-BNP) at Week 16

End point title	Change From Baseline in N-terminal Pro Brain Natriuretic Peptide (NT pro-BNP) at Week 16[7]

End point description:

NT pro-BNP is a cardiac marker, having the prognostic value for participants with heart failure or left ventricular dysfunction. Higher level of the marker was indicative of heart damage.
Efficacy analysis set included all subjects who
received at least 1 dose of study drug. Here, 'n' signifies those subjects who
were evaluable at specified time points.

End point type	Primary

End point timeframe:

Baseline, Week 16

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 analysed for this primary endpoint.

End point values	Sildenafil			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: picogram per milliliter				
arithmetic mean (standard deviation)				
Baseline (n =6)	843.03 (± 1120.9)			
Change at Week 16 (n =4)	-546.85 (± 1107.621)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Number of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point description:

An AE was any untoward medical occurrence attributed to study drug in a subjects who received study drug. An SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Treatment-emergent are events between first dose of study drug and up to 28 days after last dose that were absent before treatment or that worsened relative to pretreatment state. Safety analysis set included all subjects who

received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Baseline up to 28 days after last dose of study drug (up to 20 weeks)

End point values	Sildenafil			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: subjects				
AEs	6			
SAEs	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-Related Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Number of Subjects With Treatment-Related Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point description:

An AE was any untoward medical occurrence attributed to study drug in a subject who received study drug. An SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly.
Safety analysis set included all subjects who
received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Baseline up to 28 days after last dose of study drug (up to 20 weeks)

End point values	Sildenafil			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: subjects				
AEs	3			
SAEs	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Systolic and Diastolic Blood Pressure (BP) at Week 4, 8 and 16

End point title	Change From Baseline in Systolic and Diastolic Blood Pressure (BP) at Week 4, 8 and 16

End point description:

BP measurement is recorded as 1) Systolic blood pressure when heart is contracting and it is the maximum arterial pressure during contraction of left ventricle. 2) Diastolic BP when heart is relaxing and it is the minimum arterial pressure during relaxation and dilation of ventricles.
Safety analysis set included
all subjects who received at least 1 dose of study drug. Here, 'n' signifies those subjects who were evaluable at specified time points.

End point type	Secondary

End point timeframe:

Baseline, Week 4, 8, 16

End point values	Sildenafil			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: mmHg				
arithmetic mean (standard deviation)				
Baseline: Supine Systolic BP (n =5)	95.4 (± 13.41)			
Baseline: Supine Diastolic BP (n =5)	55.8 (± 10.87)			
Baseline: Sitting Systolic BP (n =1)	110 (± 99999)			
Baseline: Sitting Diastolic BP (n =1)	60 (± 99999)			
Change at Week 4: Supine Systolic BP (n =5)	5.6 (± 9.91)			
Change at Week 4: Supine Diastolic BP (n =5)	1.6 (± 13.65)			
Change at Week 4: Sitting Systolic BP (n =1)	16 (± 99999)			
Change at Week 4: Sitting Diastolic BP (n =1)	23 (± 99999)			
Change at Week 8: Supine Systolic BP (n =4)	7.8 (± 14.93)			
Change at Week 8: Supine Diastolic BP (n =4)	2.3 (± 12.28)			
Change at Week 8: Sitting Systolic BP (n =1)	-6 (± 99999)			
Change at Week 8: Sitting Diastolic BP(n =1)	-3 (± 99999)			
Change at Week 16: Supine Systolic BP (n =3)	7.7 (± 17.62)			
Change at Week 16: Supine Diastolic BP(n =3)	-1.3 (± 12.22)			
Change at Week 16: Sitting Systolic BP (n =1)	8 (± 99999)			
Change at Week 16: Sitting Diastolic BP (n =1)	10 (± 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Heart Rate at Week 4, 8 and 16

End point title	Change From Baseline in Heart Rate at Week 4, 8 and 16

End point description:

Safety analysis set included all subjects who received at least 1 dose of study drug. Here, 'n' signifies those subjects who were evaluable at specified time points.

End point type	Secondary

End point timeframe:

Baseline, Week 4, 8, 16

End point values	Sildenafil			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: beats per minute (bpm)				
arithmetic mean (standard deviation)				
Baseline: Supine Heart rate (n =5)	100.2 (± 15.91)			
Baseline: Sitting Heart rate (n =1)	96 (± 99999)			
Change at Week 4: Supine Heart rate (n =5)	-1 (± 12.08)			
Change at Week 4: Sitting Heart rate (n =1)	-22 (± 99999)			
Change at Week 8: Supine Heart rate (n =4)	-0.5 (± 9.11)			
Change at Week 8: Sitting Heart rate (n =1)	0 (± 99999)			
Change at Week 16: Supine Heart rate (n =3)	3 (± 28.69)			
Change at Week 16: Sitting Heart rate (n =1)	4 (± 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Laboratory Abnormalities

End point title	Number of Subjects With Laboratory Abnormalities

End point description:

Laboratory abnormality criteria: Hematology (hemoglobin, hematocrit, red blood cell count [less than {<}]0.8*lower limit of normal [LLN]; platelets <0.5*LLN, greater than [>]1.75*upper limit of normal [ULN], white blood cells <0.6*LLN, >1.5*ULN; lymphocytes, neutrophils <0.8*LLN, >1.2*ULN, eosinophils, basophils, monocytes >1.2*ULN); liver function (total and direct bilirubin >1.5*ULN, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase >3.0*ULN, total protein, albumin <0.8*LLN, >1.2*ULN); renal (creatinine, blood urea nitrogen >1.3*ULN); electrolytes (sodium <0.95*LLN, >1.05*ULN, potassium, chloride <0.9*LLN, >1.1*ULN; other (glucose <0.6*LLN or >1.5*ULN); urinalysis (dipstick) urine glucose, urine protein, urine blood/Hemoglobin, [greater than or equal to {>=}1]. Safety analysis set included all subjects who received atleast 1 dose of study drug.

End point type	Secondary

End point timeframe:

Baseline up to Week 16

End point values	Sildenafil			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: subjects	3			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Clinically Significant 12-Lead Electrocardiogram (ECG) Abnormalities

End point title	Number of Subjects With Clinically Significant 12-Lead Electrocardiogram (ECG) Abnormalities

End point description:

Criteria for clinically significant abnormality in ECG parameters: Maximum corrected QT interval (QTc) from 450 millisecond (msec) to less than (<) 480 msec, Maximum QTcB interval (Bazett's Correction) from 450 msec to <480 msec, Maximum QTcF interval (Fredericia's Correction) from 450 msec to <480 msec, maximum QTc interval increase from baseline of 30 msec to <60 msec and >=60 msec.
Safety analysis set included all subjects who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Baseline up to Week 16

End point values	Sildenafil			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: subjects	5			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Ocular Examination Abnormalities

End point title	Number of Subjects With Ocular Examination Abnormalities

End point description:

Ocular examination measures included external examination of the eye, funduscopy, assessments of visual acuity, and color vision. Ocular examination findings were considered abnormal based on investigator's decision. Safety
analysis set included all subjects who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Baseline up to Week 16

End point values	Sildenafil			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: subjects	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Pulmonary Artery Systolic and Diastolic Pressure at Week 16

End point title	Change From Baseline in Pulmonary Artery Systolic and Diastolic Pressure at Week 16

End point description:

Efficacy analysis set included all subjects who received at least 1 dose of study drug. Here, 'n' signifies those subjects who were evaluable at specified time points.

End point type	Secondary

End point timeframe:

Baseline, Week 16

End point values	Sildenafil			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: mmHg				
arithmetic mean (standard deviation)				
Baseline: Systolic Pressure (n =6)	82.5 (± 35.51)			
Baseline: Diastolic Pressure (n =6)	42 (± 18.19)			
Change at Week 16: Systolic Pressure (n =4)	-9.8 (± 18.01)			
Change at Week 16: Diastolic Pressure (n =4)	-3.5 (± 13.99)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Systemic Artery Systolic and Diastolic Pressure at Week 16

End point title	Change From Baseline in Systemic Artery Systolic and Diastolic

	Pressure at Week 16

End point description:

Efficacy analysis set included all subjects who received at least 1 dose of study drug. Here, 'n' signifies those subjects who were evaluable at specified time points.

End point type	Secondary

End point timeframe:

Baseline, Week 16

End point values	Sildenafil			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: mmHg				
arithmetic mean (standard deviation)				
Baseline: Systolic Pressure (n =6)	95.3 (± 15.2)			
Baseline: Diastolic Pressure (n =6)	60.2 (± 19.3)			
Change at Week 16: Systolic Pressure (n =4)	0.3 (± 10.21)			
Change at Week 16: Diastolic Pressure (n =4)	-1.5 (± 14.25)			

Statistical analyses

No statistical analyses for this end point

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

End point title	Change From Baseline in Pulmonary Vascular Resistance (PVR) at Week 16

End point description:

The resistance to blood flow through the pulmonary circulation is known as PVR. It is largely influenced by the caliber of the pulmonary arteries and capillaries and was measured in terms of Wood units. Wood unit =80 dyne*seconds per centimetre^5 (dyne*sec/cm^5). Efficacy analysis set included all subjects who received at least 1 dose of study drug. Here, 'n' signifies those subjects who were evaluable at specified time points.

End point type	Secondary

End point timeframe:

Baseline, Week 16

End point values	Sildenafil			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: Wood units				
arithmetic mean (standard deviation)				
Baseline (n =6)	21.372 (± 11.3408)			

Change at Week 16 (n =4)	-6.145 (± 10.3499)				

Statistical analyses

No statistical analyses for this end point

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

End point title	Change From Baseline in Right Atrial Pressure (RAP) at Week 16
End point description:	

RAP is the blood pressure in the right atrium of the heart. It reflects the amount of blood returning to the heart and the ability of the heart to pump the blood into the arterial system. RAP was measured using a pressure transducer positioned at the mid-axillary line with the subject in the supine position. Efficacy analysis set included all subjects who received at least 1 dose of study drug. Here, 'n' signifies those subjects who were evaluable at specified time points.

End point type	Secondary
End point timeframe:	

Baseline, Week 16

End point values	Sildenafil			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: mmHg				
arithmetic mean (standard deviation)				
Baseline (n =6)	6.5 (± 2.88)			
Change at Week 16 (n =4)	1.3 (± 2.36)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Pulmonary Capillary Wedge Pressure (PCWP) at Week 16

End point title	Change From Baseline in Pulmonary Capillary Wedge Pressure (PCWP) at Week 16
End point description:	

PCWP was measured by pulmonary artery catheterization and provided an indirect measure of left atrial pressure. Efficacy analysis set included all subjects who received at least 1 dose of study drug. Here, 'n' signifies those subjects who were evaluable at specified time points.

End point type	Secondary
End point timeframe:	

Baseline, Week 16

End point values	Sildenafil			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: mmHg				
arithmetic mean (standard deviation)				
Baseline (n =6)	8.5 (± 0.84)			
Change at Week 16 (n =4)	2.5 (± 1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Cardiac Output (CO) at Week 16

End point title	Change From Baseline in Cardiac Output (CO) at Week 16

End point description:

Cardiac output is simply the amount of blood pumped by the heart per minute. Efficacy analysis set included all subjects who received at least 1 dose of study drug. Here, 'n' signifies those subjects who were evaluable at specified time points.

End point type	Secondary

End point timeframe:

Baseline, Week 16

End point values	Sildenafil			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: liter per minute				
arithmetic mean (standard deviation)				
Baseline (n =6)	2.62 (± 0.9879)			
Change at Week 16 (n =4)	0.42 (± 0.9076)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Cardiac Index (CI) at Week 16

End point title	Change From Baseline in Cardiac Index (CI) at Week 16

End point description:

Cardiac index is a hemodynamic parameter that relates the cardiac output from left ventricle in one minute to BSA, thus relating heart performance to the size of the individual. CI was calculated as cardiac

output in systemic circulation divided by BSA. Efficacy analysis set included all subjects who received at least 1 dose of study drug. Here, 'n' signifies those subjects who were evaluable at specified time points.

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

End point values	Sildenafil			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: liter per minute per meter square				
arithmetic mean (standard deviation)				
Baseline (n =6)	3.07 (± 0.746)			
Change at Week 16 (n=4)	0.658 (± 1.8912)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Systemic Vascular Resistance (SVR) at Week 16

End point title	Change From Baseline in Systemic Vascular Resistance (SVR) at Week 16

End point description:

The resistance to blood flow through the systemic circulation is known as SVR. This can be used in measuring blood pressure, blood flow and cardiac function and measured in terms of Wood units. Wood unit =80 dyne*seconds per centimetre^5 (dyne*sec/cm^5). Efficacy analysis set included all subjects who received at least 1 dose of study drug. Here, 'n' signifies those subjects who were evaluable at specified time points.

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

End point values	Sildenafil			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: Wood units				
arithmetic mean (standard deviation)				
Baseline (n =6)	26.545 (± 3.0768)			
Change at Week 16 (n =4)	-3.403 (± 4.4409)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Systemic Vascular Resistance Index (SVRI) at Week 16

End point title	Change From Baseline in Systemic Vascular Resistance Index (SVRI) at Week 16

End point description:

SVRI equals systemic vascular resistance (SVR) times BSA. SVR is the resistance to blood flow through the systemic circulation and it was measured in Wood units. Wood unit =80 dyne*seconds per centimetre^5 (dyne*sec/cm^5). Efficacy analysis set included all subjects who received at least 1 dose of study drug. Here, 'n' signifies those subjects who were evaluable at specified time points.

End point type	Secondary

End point timeframe:

Baseline, Week 16

End point values	Sildenafil			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: Wood units*meter^2				
arithmetic mean (standard deviation)				
Baseline (n =6)	23.855 (± 12.148)			
Change at Week 16 (n =4)	-2.378 (± 3.9096)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Mixed Venous Oxygen Saturation (SVO2) at Week 16

End point title	Change From Baseline in Mixed Venous Oxygen Saturation (SVO2) at Week 16

End point description:

SvO2 is the percentage of mixed venous oxygen (amount of oxygen bound to hemoglobin in venous blood). Change from baseline in percentage of mixed venous oxygen was reported in this outcome measure. Efficacy analysis set included all subjects who received at least 1 dose of study drug. Here, 'n' signifies those subjects who were evaluable at specified time points.

End point type	Secondary

End point timeframe:

Baseline, Week 16

End point values	Sildenafil			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: percentage of mixed venous oxygen				
arithmetic mean (standard deviation)				
Baseline (n =6)	65.3 (± 8.549)			
Change at Week 16 (n =4)	5.38 (± 12.426)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Arterial Oxygen Saturation (SaO2) at Week 16

End point title	Change From Baseline in Arterial Oxygen Saturation (SaO2) at Week 16

End point description:

SaO2 is the percentage of arterial oxygen (amount of oxygen bound to hemoglobin in arterial blood). Change from baseline in percentage of arterial oxygen was reported in this outcome measure. Efficacy analysis set included all subjects who received at least 1 dose of study drug. Here, 'n' signifies those subjects who were evaluable at specified time points.

End point type	Secondary

End point timeframe:

Baseline, Week 16

End point values	Sildenafil			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: percentage of arterial oxygen				
arithmetic mean (standard deviation)				
Baseline (n =6)	95.08 (± 2.73)			
Change at Week 16 (n =4)	-0.8 (± 1.691)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Maximum Observed Plasma Concentration (Cmax) of Sildenafil and UK-103,320

End point title	Maximum Observed Plasma Concentration (Cmax) of Sildenafil and UK-103,320

End point description:

UK-103,320 was the main metabolite of Sildenafil and was produced by cytochrome P450 3A4. Pharmacokinetic (PK) parameter analysis set included all subjects who have at least 1 of PK parameters of interest.

End point type	Other pre-specified
End point timeframe:	
Pre-dose (0 hour) on Week 4, 8, 16 and 1, 2, 4, 8 hours post-dose on Week 16	

End point values	Sildenafil			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: nanogram per milliliter				
geometric mean (geometric coefficient of variation)				
Sildenafil	138.1 (± 73)			
UK-103,320	73.66 (± 48)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Area Under the Curve From Time Zero to End of Dosing Interval (AUCtau) of Sildenafil and UK-103,320

End point title	Area Under the Curve From Time Zero to End of Dosing Interval (AUCtau) of Sildenafil and UK-103,320
End point description:	
UK-103,320 was the main metabolite of Sildenafil and was produced by cytochrome P450 3A4. PK parameter analysis set included all subjects who have at least 1 of PK parameters of interest.	
End point type	Other pre-specified
End point timeframe:	
Pre-dose (0 hour) on Week 4, 8, 16 and 1, 2, 4, 8 hours post-dose on Week 16	

End point values	Sildenafil			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: nanogram*hour per millimeter				
geometric mean (geometric coefficient of variation)				
Sildenafil	338.9 (± 54)			
UK-103,320	210.2 (± 74)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Time to Reach Maximum Observed Plasma Concentration

(Tmax) of Sildenafil and UK-103,320

End point title	Time to Reach Maximum Observed Plasma Concentration (Tmax) of Sildenafil and UK-103,320

End point description:

UK-103,320 was the main metabolite of Sildenafil and was produced by cytochrome P450 3A4. PK parameter analysis set included all subjects who have at least 1 of PK parameters of interest.

End point type	Other pre-specified

End point timeframe:

Pre-dose (0 hour) on Week 4, 8, 16 and 1, 2, 4, 8 hours post-dose on Week 16

End point values	Sildenafil			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: hour				
median (full range (min-max))				
Sildenafil	1 (1 to 1.97)			
UK-103,320	1 (1 to 1.97)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Terminal Half Life (t1/2) of Sildenafil and UK-103,320

End point title	Terminal Half Life (t1/2) of Sildenafil and UK-103,320

End point description:

Terminal half-life is the time measured for the plasma concentration to decrease by one half of its original concentration. UK-103,320 was a main metabolite of sildenafil and was produced by cytochrome P450 3A4. PK parameter analysis set included all subjects who have at least 1 of PK parameters of interest.

End point type	Other pre-specified

End point timeframe:

Pre-dose (0 hour) on Week 4, 8, 16 and 1, 2, 4, 8 hours post-dose on Week 16

End point values	Sildenafil			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: hour				
median (full range (min-max))				
Sildenafil (n =2)	1.785 (1.63 to 1.94)			
UK-103,320 (n =3)	2.11 (2.04 to 3.26)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Apparent Oral Clearance (CL/F) of Sildenafil

End point title	Apparent Oral Clearance (CL/F) of Sildenafil
End point description:	
Clearance of a drug is a measure of the rate at which a drug is metabolized or eliminated by normal biological processes. PK parameter analysis set included all subjects who have at least 1 of PK parameters of interest.	
End point type	Other pre-specified
End point timeframe:	
Pre-dose (0 hour) on Week 4, 8, 16 and 1, 2, 4, 8 hours post-dose on Week 16	

End point values	Sildenafil			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: liter per hour				
geometric mean (geometric coefficient of variation)	41.73 (± 77)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Apparent Volume of Distribution (Vz/F) of Sildenafil

End point title	Apparent Volume of Distribution (Vz/F) of Sildenafil
End point description:	
Volume of distribution is defined as the theoretical volume in which the total amount of drug would need to be uniformly distributed to produce the desired plasma concentration of a drug. Apparent volume of distribution after oral dose (Vz/F) is influenced by the fraction absorbed. PK parameter analysis set included all subjects who have at least 1 of PK parameters of interest. Here,'N' signifies those subjects who were evaluable for this measure.	
End point type	Other pre-specified
End point timeframe:	
Pre-dose (0 hour) on Week 4, 8, 16 and 1, 2, 4, 8 hours post-dose on Week 16	

End point values	Sildenafil			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: liter				
median (full range (min-max))	77.9 (62.4 to 93.4)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline in Ratio of Acceleration Time to Ejection Time (AcT/ET) at Week 16

End point title	Change From Baseline in Ratio of Acceleration Time to Ejection Time (AcT/ET) at Week 16
End point description:	

Acceleration time and ejection time are quantitative Doppler parameters and ratio of acceleration time to ejection time is a useful tool to evaluate the severity of aortic stenosis. Efficacy analysis set included all subjects who received at least 1 dose of study drug. Here, 'n' signifies those subjects who were evaluable at specified time points.

End point type	Other pre-specified
End point timeframe:	

Baseline, Week 16

End point values	Sildenafil			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: ratio				
arithmetic mean (standard deviation)				
Baseline (n =6)	0.3038 (± 0.09675)			
Change at Week 16 (n =4)	0.0175 (± 0.10261)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline in Right Ventricular Tei Index at Week 16

End point title	Change From Baseline in Right Ventricular Tei Index at Week 16
End point description:	

The right ventricular Tei Index is an index of myocardial performance. It is defined as the sum of isovolumic contraction time and isovolumic relaxation time divided by the ejection time. Efficacy analysis set included all subjects who received at least 1 dose of study drug. Here, 'n' signifies those subjects who were evaluable at specified time points.

End point type	Other pre-specified
End point timeframe:	
Baseline, Week 16	

End point values	Sildenafil			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: ratio				
arithmetic mean (standard deviation)				
Baseline (n =3)	0.754 (± 0.48602)			
Change at Week 16 (n =2)	-0.044 (± 0.37618)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline in Right Ventricular Size at Week 16

End point title	Change From Baseline in Right Ventricular Size at Week 16
End point description:	
Efficacy analysis set included all subjects who received at least 1 dose of study drug. Here, 'n' signifies those subjects who were evaluable at specified time points.	
End point type	Other pre-specified
End point timeframe:	
Baseline, Week 16	

End point values	Sildenafil			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: centimeter (cm)				
arithmetic mean (standard deviation)				
Baseline (n =6)	3.37 (± 1.216)			
Change at Week 16 (n=4)	-0.4 (± 0.408)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline in Tricuspid Valve Annulus Size at Week 16

End point title	Change From Baseline in Tricuspid Valve Annulus Size at Week 16
End point description:	
The tricuspid valve lies between the right atrium and the right ventricle and is placed in a more apical position than the mitral valve. The annulus separates the right atrium from the right ventricle. Efficacy analysis set included all subjects who received at least 1 dose of study drug. Here, 'n' signifies those subjects who were evaluable at specified time points.	
End point type	Other pre-specified
End point timeframe:	
Baseline, Week 16	

End point values	Sildenafil			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: cm				
arithmetic mean (standard deviation)				
Baseline (n =6)	2.19 (± 0.5636)			
Change at Week 16 (n =4)	-0.103 (± 0.3727)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline in Tricuspid Regurgitation - Pressure Gradient (TR-PG) Peak at Week 16

End point title	Change From Baseline in Tricuspid Regurgitation - Pressure Gradient (TR-PG) Peak at Week 16
End point description:	
Tricuspid regurgitation (insufficiency) is the failure of the tricuspid valve to close properly during systole, leading to the leaking of blood from the right ventricle into the right atrium. Efficacy analysis set included all subjects who received at least 1 dose of study drug. Here, 'n' signifies those subjects who were evaluable at specified time points.	
End point type	Other pre-specified
End point timeframe:	
Baseline, Week 16	

End point values	Sildenafil			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: mmHg				
arithmetic mean (standard deviation)				
Baseline (n =5)	73 (± 39.31)			
Change at Week 16 (n =2)	-6 (± 33.94)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline in Pulmonary Regurgitation - Pressure Gradient (PR-PG) End-Diastole at Week 16

End point title	Change From Baseline in Pulmonary Regurgitation - Pressure Gradient (PR-PG) End-Diastole at Week 16

End point description:

Pulmonary regurgitation (PR) or insufficiency is a valvular heart disease characterized by an incomplete closure of the pulmonary valve leading to a diastolic reflux into the right ventricle. Efficacy analysis set included all subjects who received at least 1 dose of study drug. Here, 'n' signifies those subjects who were evaluable at specified time points.

End point type	Other pre-specified

End point timeframe:

Baseline, Week 16

End point values	Sildenafil			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: mmHg				
arithmetic mean (standard deviation)				
Baseline (n =3)	29 (± 14.73)			
Change at Week 16 (n =2)	3.5 (± 13.44)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Pericardial Effusion

End point title	Number of Subjects With Pericardial Effusion

End point description:

Pericardial effusion is the presence of an abnormal amount of fluid in the pericardial cavity, as determined by echocardiography. Efficacy analysis set included all subjects who received at least 1 dose of study drug.

End point type	Other pre-specified

End point timeframe:

Baseline up to Week 16

End point values	Sildenafil			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: subjects	0			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline in Tricuspid Annular Plane Systolic Excursion (TAPSE) at Week 16

End point title	Change From Baseline in Tricuspid Annular Plane Systolic Excursion (TAPSE) at Week 16

End point description:

Tricuspid annular plane systolic excursion is a parameter depicting global right ventricular function. Efficacy analysis set included all subjects who received at least 1 dose of study drug. Here, 'n' signifies those subjects who were evaluable at specified time points.

End point type	Other pre-specified

End point timeframe:

Baseline, Week 16

End point values	Sildenafil			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: cm				
arithmetic mean (standard deviation)				
Baseline (n =6)	1.47 (± 0.437)			
Change at Week 16 (n =4)	0.18 (± 0.32)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:	
Baseline up to 28 days after last dose of study drug (up to 20 weeks)	
Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Sildenafil
Reporting group description:	

Subjects received 10 milligram (mg) or 20 mg of Sildenafil (based on their body weight) orally, thrice daily on Day 1 (Baseline), Week 4, 8 and 16. Subjects with less than or equal to (<=) 20 kilogram (kg) of body weight received 10 mg dose, thrice daily as powder for oral suspension and subjects with greater than (>) 20 kg of body weight received 20 mg dose, thrice daily as film-coated tablets.

Serious adverse events	Sildenafil		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 6 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Sildenafil		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)		
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	2		
Alanine aminotransferase increased			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	2		
Ammonia increased			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		

Weight increased			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 6 (33.33%)		
occurrences (all)	4		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Feeling abnormal			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Eye disorders			
Conjunctivitis allergic			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Gastrointestinal disorders			
Dental caries			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	2 / 6 (33.33%)		
occurrences (all)	2		
Vomiting			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Reproductive system and breast disorders			

Dysmenorrhoea	Additional description: As the event is gender specific, only female participants were evaluated.		
subjects affected / exposed[1]	1 / 3 (33.33%)		
occurrences (all)	1		
Erection increased	Additional description: As the event is gender specific, only female participants were evaluated.		
subjects affected / exposed[2]	1 / 3 (33.33%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Pulmonary arterial hypertension			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Rhinitis allergic			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Dermatitis diaper			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Dry skin			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Eczema			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 6 (33.33%)		
occurrences (all)	3		

Gastroenteritis			
subjects affected / exposed	2 / 6 (33.33%)		
occurrences (all)	2		
Influenza			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	3 / 6 (50.00%)		
occurrences (all)	6		
Nasopharyngitis			
subjects affected / exposed	2 / 6 (33.33%)		
occurrences (all)	4		

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: As the event is gender specific, only female participants were evaluated.

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: As the event is gender specific, only female participants were evaluated.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 August 2012	Addition of Part 2 (Long- term administration of the investigational drug)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

 None reported