



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	12 March 2018

Results information

Result version number	v3 (current)
This version publication date	30 August 2018
First version publication date	24 November 2016
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	A1481298
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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, NY 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 8007181021, 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	Final
Date of interim/final analysis	20 April 2018
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	12 March 2018
Was the trial ended prematurely?	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:

The study was conducted at 3 sites in Japan. Data reported is based on data cut-off date of 26 December 2016.

Period 1

Period 1 title	Part 1 (Screening till Week 16)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Sildenafil
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Arm description:

Subjects received 10 milligram (mg) or 20 mg of Sildenafil (based on their body weight) orally, thrice daily on Day 1 (Baseline), Weeks 4, 8, and 16 in Part 1 of the study. Subjects who completed Part 1 and required continuing treatment with Sildenafil, received 10 mg or 20 mg of Sildenafil (based on their body weight) orally, thrice daily on Weeks 28, 40, 52 and thereafter every 12 weeks until Sildenafil obtained marketing approval (up to a maximum of 119.6 weeks). Subjects with less than or equal to ($\leq$) 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 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, Weeks 4, 8 and 16

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, Weeks 4, 8 and 16

Number of subjects in period 1	Sildenafil
Started	6
Completed	3
Not completed	3
Insufficient clinical response	3

Period 2	
Period 2 title	Part 2(Week17 to maximum of 119.6 weeks)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Sildenafil
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Arm description:

Subjects received 10 milligram (mg) or 20 mg of Sildenafil (based on their body weight) orally, thrice daily on Day 1 (Baseline), Weeks 4, 8, and 16 in Part 1 of the study. Subjects who completed Part 1 and required continuing treatment with Sildenafil, received 10 mg or 20 mg of Sildenafil (based on their body weight) orally, thrice daily on Weeks 28, 40, 52 and thereafter every 12 weeks until Sildenafil obtained marketing approval (up to a maximum of 119.6 weeks). Subjects with less than or equal to ($\leq$) 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 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 Weeks 28, 40, 52 and thereafter every 12 weeks until Sildenafil obtained marketing approval (up to a maximum of 119.6 weeks).

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 Weeks 28, 40, 52 and thereafter every 12 weeks until Sildenafil obtained marketing approval (up to a maximum of 119.6 weeks).

Number of subjects in period 2	Sildenafil
Started	3
Completed	1
Not completed	2
Coil Embolization	1
Change of treatment plan	1

Baseline characteristics

Reporting groups

Reporting group title	Sildenafil
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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), Weeks 4, 8, and 16 in Part 1 of the study. Subjects who completed Part 1 and required continuing treatment with Sildenafil, received 10 mg or 20 mg of Sildenafil (based on their body weight) orally, thrice daily on Weeks 28, 40, 52 and thereafter every 12 weeks until Sildenafil obtained marketing approval (up to a maximum of 119.6 weeks). Subjects with less than or equal to ($\leq$) 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	-	
Sex: Female, Male			
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), Weeks 4, 8, and 16 in Part 1 of the study. Subjects who completed Part 1 and required continuing treatment with Sildenafil, received 10 mg or 20 mg of Sildenafil (based on their body weight) orally, thrice daily on Weeks 28, 40, 52 and thereafter every 12 weeks until Sildenafil obtained marketing approval (up to a maximum of 119.6 weeks). Subjects with less than or equal to ($\leq$) 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 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), Weeks 4, 8, and 16 in Part 1 of the study. Subjects who completed Part 1 and required continuing treatment with Sildenafil, received 10 mg or 20 mg of Sildenafil (based on their body weight) orally, thrice daily on Weeks 28, 40, 52 and thereafter every 12 weeks until Sildenafil obtained marketing approval (up to a maximum of 119.6 weeks). Subjects with less than or equal to ($\leq$) 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) ($PVRI = PVR \times BSA$). 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' = subjects evaluable for this end point 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 analyzed for this 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 ($\pm$ 11.7629)			
Change at Week 16 (n =4)	-4.113 ($\pm$ 6.3770)			

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]
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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' = subjects evaluable for this end point at specified time points.

End point type	Primary
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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 analyzed for this endpoint.

End point values	Sildenafil			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: millimeter 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]
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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
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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 analyzed for this 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]
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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' (Number of Subjects Analyzed) signifies those subjects who were evaluable for this endpoint.

End point type	Primary
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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 analyzed for this 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]
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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, Number of subjects analyzed signifies those subjects who were evaluable for this endpoint.

End point type	Primary
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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 analyzed for this 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]
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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' = subjects evaluable for this end point at specified time points.

End point type	Primary
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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 analyzed for this 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 ($\pm$ 135.080)			
Change at Week 16 (n =4)	-64.10 ($\pm$ 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]
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End point description:

NT pro-BNP is a cardiac marker, having the prognostic value for subjects 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' = subjects evaluable for this end point at specified time points.

End point type	Primary
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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 analyzed for this 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 ($\pm$ 1120.900)			
Change at Week 16 (n =4)	-546.85 ($\pm$ 1107.621)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in World Health Organization (WHO) Functional Class in Subjects With Pulmonary Arterial Hypertension (PAH) at Weeks 28, 40, 52, 64, 76, 88, 100, 112 and 124

End point title	Change From Baseline in World Health Organization (WHO) Functional Class in Subjects With Pulmonary Arterial
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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 was used in this analysis. Here, Number of subjects analyzed specifies number of subjects who completed Part 1 of the study and continued treatment with Sildenafil in Part 2 of the study and 'n' = subjects evaluable for this endpoint for specified categories.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 4, 8, 16, 28, 40, 52, 64, 76, 88, 100, 112 and 124

End point values	Sildenafil			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: subjects				
Baseline: Class I (n =3)	2			
Baseline: Class II (n =3)	3			
Baseline: Class III (n =3)	1			
Baseline: Class IV (n =3)	0			
Week 28: Improved (n =3)	1			
Week 28: No Change (n =3)	2			
Week 28: Worsened (n =3)	0			
Week 40: Improved (n =3)	1			
Week 40: No Change (n =3)	2			
Week 40: Worsened (n =3)	0			
Week 52: Improved (n =3)	1			
Week 52: No Change (n =3)	2			
Week 52: Worsened (n =3)	0			
Week 64: Improved (n =2)	1			
Week 64: No Change (n =2)	1			
Week 64: Worsened (n =2)	0			
Week 76: Improved (n =2)	1			
Week 76: No Change (n =2)	0			
Week 76: Worsened (n =2)	1			
Week 88: Improved (n =1)	1			
Week 88: No Change (n =1)	0			
Week 88: Worsened (n =1)	0			
Week 100: Improved (n =1)	1			
Week 100: No Change (n =1)	0			
Week 100: Worsened (n =1)	0			
Week 112: Improved (n =1)	1			
Week 112: No Change (n =1)	0			
Week 112: Worsened (n =1)	0			
Week 124: Improved (n =1)	1			
Week 124: No Change (n =1)	0			
Week 124:Worsened (n =1)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Brain Natriuretic Peptide (BNP) at Week 52 and End of Treatment (EOT)

End point title	Change From Baseline in Brain Natriuretic Peptide (BNP) at Week 52 and End of Treatment (EOT)
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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 'Number of subjects analyzed' specifies number of subjects who completed Part 1 of the study and continued treatment with Sildenafil in Part 2 of the study.

End point type	Secondary
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End point timeframe:

Baseline, Week 52 and End of treatment (maximum duration of treatment: 119.6 weeks)

End point values	Sildenafil			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: picograms per milliliter				
arithmetic mean (standard deviation)				
Baseline	100.17 ($\pm$ 151.478)			
Change at Week 52	-85.17 ($\pm$ 55.088)			
Change at EoT	-85.17 ($\pm$ 155.088)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in N-terminal Pro Brain Natriuretic Peptide (NT pro-BNP) at Week 52 and End of Treatment (EOT)

End point title	Change From Baseline in N-terminal Pro Brain Natriuretic Peptide (NT pro-BNP) at Week 52 and End of Treatment (EOT)
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End point description:

NT pro-BNP is a cardiac marker, having the prognostic value for subjects 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 'Number of subjects analyzed' specifies number of subjects who completed Part 1 of the study and continued treatment with Sildenafil in Part 2 of the study.

End point type	Secondary
End point timeframe:	
Baseline, Week 52 and End of treatment (maximum duration of treatment: 119.6 weeks)	

End point values	Sildenafil			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: picograms per milliliter				
arithmetic mean (standard deviation)				
Baseline	841.73 (± 1323.533)			
Change at Week 52	-754.90 (± 1335.370)			
Change at EoT	-754.90 (± 1335.370)			

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 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. 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 pre-treatment state. AEs included both SAEs and non-serious AEs. Safety analysis set included all subjects who received at least 1 dose of study drug.	
End point type	Secondary
End point timeframe:	
Baseline upto 28 days after last dose of study drug (maximum duration of treatment: 119.6 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-Emergent Treatment-Related Adverse Events (AEs) and Serious Adverse Events (SAEs)

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

Treatment-related 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. 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 pre-treatment state. AEs included both SAEs and non-serious AEs. Safety analysis set included all subjects who received at least 1 dose of study drug.

End point type	Secondary
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End point timeframe:

Baseline upto 28 days after last dose of study drug (maximum duration of treatment: 119.6 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 Weeks 4, 8, 16, 28, 40, 52, 64, 76, 88, 100, 112 and 124

End point title	Change From Baseline in Systolic and Diastolic Blood Pressure (BP) at Weeks 4, 8, 16, 28, 40, 52, 64, 76, 88, 100, 112 and 124
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End point description:

BP measurement is recorded as supine and sitting systolic and diastolic systemic blood pressure: 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. Only those categories in which at least 1 subject had data were reported. Safety analysis set included all subjects who received at least 1 dose of study drug. Here, 'n' = Subjects evaluable for this endpoint for specified categories. Standard deviation was not analyzed since only 1 subject was evaluable and has been denoted by '99999'.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 4, 8, 16, 28, 40, 52, 64, 76, 88, 100, 112 and 124

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)	110.0 (± 99999)			
Baseline: Sitting Diastolic BP (n =1)	60.0 (± 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)	16.0 (± 99999)			
Change at Week 4: Sitting Diastolic BP (n =1)	23.0 (± 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)	-6.0 (± 99999)			
Change at Week 8: Sitting Diastolic BP (n =1)	-3.0 (± 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)	8.0 (± 99999)			
Change at Week 16: Sitting Diastolic BP (n =1)	10.0 (± 99999)			
Change at Week 28: Supine Systolic BP (n =3)	7.0 (± 19.31)			
Change at Week 28: Supine Diastolic BP (n =3)	1.7 (± 9.29)			
Change at Week 40: Supine Systolic BP (n =2)	-7.5 (± 3.54)			
Change at Week 40: Supine Diastolic BP (n =2)	2.0 (± 0.00)			
Change at Week 52: Supine Systolic BP (n =2)	2.0 (± 15.56)			
Change at Week 52: Supine Diastolic BP (n =2)	10.0 (± 5.66)			
Change at Week 64: Supine Systolic BP (n =1)	1.0 (± 99999)			
Change at Week 64: Supine Diastolic BP (n =1)	8.0 (± 99999)			
Change at Week 76: Supine Systolic BP (n =1)	-13.0 (± 99999)			
Change at Week 76: Supine Diastolic BP (n =1)	3.0 (± 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Heart Rate at Weeks 4, 8, 16, 28, 40, 52, 64, 76, 88, 100, 112 and 124

End point title	Change From Baseline in Heart Rate at Weeks 4, 8, 16, 28, 40, 52, 64, 76, 88, 100, 112 and 124
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End point description:

Only those categories in which at least 1 subject had data were reported. Safety analysis set included all subjects who received at least 1 dose of study drug. Here, 'n' = Subjects evaluable for this endpoint for specified categories. Standard deviation was not analyzed since only 1 subject was evaluable and has been denoted by '99999'.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 4, 8, 16, 28, 40, 52, 64, 76, 88, 100, 112 and 124

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)	96.0 (± 99999)			
Change at Week 4: Supine Heart rate (n =5)	-1.0 (± 12.08)			
Change at Week 4: Sitting Heart rate (n =1)	-22.0 (± 99999)			
Change at Week 8: Supine Heart rate (n =4)	-0.5 (± 9.11)			
Change at Week 8: Sitting Heart rate (n =1)	0.0 (± 99999)			
Change at Week 16: Supine Heart rate (n =3)	3.0 (± 28.69)			
Change at Week 16: Sitting Heart rate (n =1)	4.0 (± 99999)			
Change at Week 28: Supine Heart rate (n =3)	6.7 (± 14.36)			
Change at Week 40: Supine Heart rate (n =2)	10.0 (± 16.97)			
Change at Week 52: Supine Heart rate (n =2)	-2.0 (± 11.31)			
Change at Week 64: Supine Heart rate (n =1)	17.0 (± 99999)			
Change at Week 76: Supine Heart rate (n =1)	-8.0 (± 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 at least 1 dose of study drug.	
End point type	Secondary
End point timeframe: Baseline up-to End of treatment (maximum duration of treatment: 119.6 weeks)	

End point values	Sildenafil			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: subjects	4			

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. Here, 'n' = Subjects evaluable for this endpoint for specified categories.	
End point type	Secondary
End point timeframe: Screening, Week 16, Week 52 and End of treatment (maximum duration of treatment: 119.6 weeks)	

End point values	Sildenafil			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: subjects				
Screening (n =6)	4			
Week 16 (n =6)	5			
Week 52 (n =2)	1			
End of Treatment (n =3)	1			

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: Screening up to end of treatment (maximum duration of treatment: 119.6 weeks)	

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' = Subjects evaluable for this endpoint 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)	42.0 (± 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
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End point description:

Efficacy analysis set included all subjects who received at least 1 dose of study drug. Here, 'n' = Subjects evaluable for this endpoint at specified time points.

End point type	Secondary
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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 (± 15.20)			
Baseline: Diastolic Pressure (n =6)	60.2 (± 19.30)			
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
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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 centimetre⁵ (dyne*sec/cm⁵). Efficacy analysis set included all subjects who received at least 1 dose of study drug. Here, 'n' = Subjects evaluable for this endpoint at specified time points.

End point type	Secondary
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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
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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' = Subjects evaluable for this endpoint at specified time points.

End point type	Secondary
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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
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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' = Subjects evaluable for this endpoint at specified time points.

End point type	Secondary
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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 (± 1.00)			

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
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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' = Subjects evaluable for this endpoint at specified time points.

End point type	Secondary
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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)	2.620 (± 0.9879)			
Change at Week 16 (n =4)	0.420 (± 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' = Subjects evaluable for this endpoint 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)	3.070 (± 0.7460)			
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)
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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 = $80 \text{ dyne} \cdot \text{seconds per centimetre}^5$ ($\text{dyne} \cdot \text{sec}/\text{cm}^5$). Efficacy analysis set included all subjects who received at least 1 dose of study drug. Here, 'n' = Subjects evaluable for this endpoint at specified time points.

End point type	Secondary
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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 ($\pm$ 3.0768)			
Change at Week 16 (n =4)	-3.403 ($\pm$ 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
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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 = $80 \text{ dyne} \cdot \text{seconds per centimetre}^5$ ($\text{dyne} \cdot \text{sec}/\text{cm}^5$). Efficacy analysis set included all subjects who received at least 1 dose of study drug. Here, 'n' = Subjects evaluable for this endpoint at specified time points.

End point type	Secondary
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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 ($\pm$ 12.1480)			
Change at Week 16 (n =4)	-2.378 ($\pm$ 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
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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 endpoint. Efficacy analysis set included all subjects who received at least 1 dose of study drug. Here, 'n' = Subjects evaluable for this endpoint at specified time points.

End point type	Secondary
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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)	65.30 (± 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
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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 endpoint. Efficacy analysis set included all subjects who received at least 1 dose of study drug. Here, 'n' = Subjects evaluable for this endpoint at specified time points.

End point type	Secondary
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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 (± 2.730)			
Change at Week 16 (n =4)	-0.80 (± 1.691)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Maximum Observed Plasma Concentration (C_{max}) of Sildenafil and UK-103,320

End point title	Maximum Observed Plasma Concentration (C _{max}) of Sildenafil and UK-103,320
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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
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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 (ng/mL)				
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 (AUC_{tau}) of Sildenafil and UK-103,320

End point title	Area Under the Curve From Time Zero to End of Dosing
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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	1.00 (1.00 to 1.97)			
UK-103,320	1.00 (1.00 to 1.97)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Terminal Half Life (t_{1/2}) of Sildenafil and UK-103,320

End point title	Terminal Half Life (t _{1/2}) of Sildenafil and UK-103,320
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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. Here, 'n' = Subjects evaluable for this endpoint at specified time points.

End point type	Other pre-specified
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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)	2.110 (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
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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
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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: 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
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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' = Subjects evaluable for this endpoint at specified time points.

End point type	Other pre-specified
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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: Apparent Volume of Distribution (V_z/F) of Sildenafil

End point title	Apparent Volume of Distribution (V _z /F) of Sildenafil
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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 (V_z/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, Number of subjects analyzed signifies those subjects who were evaluable for this endpoint.

End point type	Other pre-specified
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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))	77.90 (62.4 to 93.4)			

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' = Subjects evaluable for this endpoint 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)	0.7540 (± 0.48602)			
Change at Week 16 (n =2)	-0.0440 (± 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' =	

Subjects evaluable for this endpoint 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)	-0.40 (± 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
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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. Change from baseline in tricuspid valve annulus size (in cm) was reported in this endpoint. Efficacy analysis set included all subjects who received at least 1 dose of study drug. Here, 'n' = Subjects evaluable for this endpoint 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)	2.190 (± 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
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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. Change from baseline in TR-PG peak (in mmHg) was reported in this endpoint. Efficacy analysis set included all subjects who received at least 1 dose of study drug. Here, 'n' = Subjects evaluable for this endpoint at specified time points.

End point type	Other pre-specified
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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)	73.0 (± 39.31)			
Change at Week 16 (n =2)	-6.0 (± 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
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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. Change from baseline in PR-PG end-diastole (in mmHg) was reported in this endpoint. Efficacy analysis set included all subjects who received at least 1 dose of study drug. Here, 'n' = Subjects evaluable for this endpoint at specified time points.

End point type	Other pre-specified
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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)	29.0 (± 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. Change from baseline in TAPSE (in cm) was reported in this endpoint. Efficacy analysis set included all subjects who received at least 1 dose of study drug. Here, 'n' = Subjects evaluable for this endpoint 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 (± 0.320)			

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 (maximum duration of treatment: 119.6 weeks)

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.1
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Reporting groups

Reporting group title	Sildenafil
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Reporting group description:

Subjects received 10 mg or 20 mg of Sildenafil (based on their body weight) orally, thrice daily on Day 1 (Baseline), Weeks 4, 8, and 16 in Part 1 of the study. Subjects who completed Part 1 and required continuing treatment with Sildenafil, received 10 mg or 20 mg of Sildenafil (based on their body weight) orally, thrice daily on Weeks 28, 40, 52 and thereafter every 12 weeks until Sildenafil obtained marketing approval (up to a maximum of 119.6 weeks). Subjects with ≤ 20 kg of body weight received 10 mg dose, thrice daily as powder for oral suspension and subjects with > 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			

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			
Ammonia increased			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	2		
Alanine aminotransferase increased			

subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 2		
Weight increased subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Blood urine present subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Vascular disorders Flushing subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Cardiac disorders Cardiac failure subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	2 / 6 (33.33%) 7		
General disorders and administration site conditions Chest pain subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Feeling abnormal subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Eye disorders Conjunctivitis allergic subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Visual acuity reduced transiently subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Vision blurred			

subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Dental caries			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	2 / 6 (33.33%)		
occurrences (all)	2		
Colitis			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	2		
Reproductive system and breast disorders			
Dysmenorrhoea	Additional description: As the event is gender specific, only female subjects were evaluated.		
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Erection increased	Additional description: As the event is gender specific, only female subjects were evaluated.		
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Rhinitis allergic			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Epistaxis			
subjects affected / exposed	2 / 6 (33.33%)		
occurrences (all)	2		
Pulmonary arterial hypertension			
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		
Dry skin			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Dermatitis diaper			
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		
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Infections and infestations			
Influenza			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Gastroenteritis			
subjects affected / exposed	2 / 6 (33.33%)		
occurrences (all)	2		
Nasopharyngitis			
subjects affected / exposed	3 / 6 (50.00%)		
occurrences (all)	6		
Bronchitis			
subjects affected / exposed	3 / 6 (50.00%)		
occurrences (all)	4		
Upper respiratory tract infection			
subjects affected / exposed	3 / 6 (50.00%)		
occurrences (all)	6		
Molluscum contagiosum			

subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Streptococcal infection			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		

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)
20 January 2016	Changed the target sample size of subjects.
25 August 2017	Addition that after approval for additional indication for pediatric PAH, "clinical study" was read as "post-marketing clinical study", Changed the treatment period of Part 2.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

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Notes: