Clinical trial results:
A multiple ascending dose study of Tadalafil to assess the pharmacokinetics and safety in a pediatric population with Pulmonary Arterial Hypertension

Summary

EudraCT number	2011-001873-24
Trial protocol	ES GB PL
Global end of trial date	03 April 2019

Results information

Result version number	v1 (current)
This version publication date	13 October 2019
First version publication date	13 October 2019

Trial information

Trial identification

Sponsor protocol code	H6D-MC-LVIG

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01484431
WHO universal trial number (UTN)	-
Other trial identifiers	Trial Number: 12917

Notes:

Sponsors

Sponsor organisation name	Eli Lilly and Company
Sponsor organisation address	Lilly Corporate Center, Indianapolis, IN, United States, 46285
Public contact	Available Mon Fri 9 AM 5 PM EST, Eli Lilly and Company, 1 877CTLilly,
Scientific contact	Available Mon Fri 9 AM 5 PM EST, Eli Lilly and Company, 1 8772854559,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000452-PIP02-10
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	03 April 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 April 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to see how much study drug is in the blood of children with pulmonary arterial hypertension (PAH) after dosing to establish the correct dose for further clinical research.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonization (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy:

Some participants received endothelin receptor agonist (ERA) background therapy (bosentan or ambrisentan).

Evidence for comparator: -

Actual start date of recruitment	17 July 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	United States: 2
Country: Number of subjects enrolled	Poland: 5
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Spain: 2
Worldwide total number of subjects	19
EEA total number of subjects	12

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0

Children (2-11 years)	13
Adolescents (12-17 years)	6
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Per protocol, the summary was based on weight cohorts.

Pre-assignment

Screening details:

This study contains 2 periods: Pharmacokinetics(PK)/safety Period 1 and an open-label safety extension Period 2. Period 1 is approximately 10 weeks (that is, approximately 5 consecutive weeks for each dose [low and high]). Period 2 is at least 2 years after participating in Period 1. Period 2 final data will be reported after study completion.

Period 1

Period 1 title	Period 1: Low Dose and High Dose
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Light Weight: <25 kg

Arm description:

Period 1: 2 milligram (mg) or 4 mg tadalafil administered once daily (QD) in oral suspension formulation for 5 weeks then 8 mg,10 mg,15 mg or 20 mg tadalafil was administered QD in oral suspension formulation for 5 weeks.

Arm type	Experimental
Investigational medicinal product name	Tadalafil
Investigational medicinal product code	
Other name	LY450190
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

Period 1: 2 milligram (mg) or 4 mg tadalafil administered once daily (QD) in oral suspension formulation for 5 weeks then 8 mg,10 mg,15 mg or 20 mg tadalafil was administered QD in oral suspension formulation for 5 weeks.

Arm title	Middle Weight: 25 kg to <40 kg

Arm description:

Period 1: 5 mg tadalafil tablet administered QD for 5 weeks then 10 mg, 15 mg or 20 mg tablet tadalafil administered QD for 5 weeks.

Arm type	Experimental
Investigational medicinal product name	Tadalafil
Investigational medicinal product code	
Other name	LY450190
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Period 1: 5 mg tadalafil tablet administered QD for 5 weeks then 10 mg, 15 mg or 20 mg tablet tadalafil administered QD for 5 weeks.

Arm title	Heavy Weight: ≥40 kg

Arm description:

Period 1: 10 mg tadalafil tablet administered QD for 5 weeks then 20 mg or 40 mg tablet tadalafil administered QD for 5 weeks.

Arm type	Experimental
Investigational medicinal product name	Tadalafil
Investigational medicinal product code	
Other name	LY450190
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Period 1: 10 mg tadalafil tablet administered QD for 5 weeks then 20 mg or 40 mg tablet tadalafil administered QD for 5 weeks.

Number of subjects in period 1	Light Weight: <25 kg	Middle Weight: 25 kg to <40 kg	Heavy Weight: ≥40 kg
Started	6	7	6
Received 2 mg Low Dose	1 [1]	0 [2]	0 [3]
Received 4 mg Low Dose	5 [4]	0 [5]	0 [6]
Received 5 mg Low Dose	0 [7]	7	0 [8]
Received 10 mg Low Dose	0 [9]	0 [10]	6
Received 8 mg High Dose	1 [11]	0 [12]	0 [13]
Received 10 mg High Dose	1 [14]	1 [15]	0 [16]
Received 15 mg High Dose	1 [17]	1 [18]	0 [19]
Received 20 mg High Dose	3 [20]	5 [21]	1 [22]
Received 40 mg High Dose	0 [23]	0 [24]	5 [25]
Completed	6	6	6
Not completed	0	1	0
Physician decision	-	1	-

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Participants in each of the three arms (Light Weight: <25 kg , Middle Weight: 25 kg to <40 kg and Heavy Weight: ≥40 kg) received different doses of drug during Low dose period 1, high dose period 1 and Period 2 therefore the numbers in the milestones individually do not add up to number started.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Participants in each of the three arms (Light Weight: <25 kg , Middle Weight: 25 kg to <40 kg and Heavy Weight: ≥40 kg) received different doses of drug during Low dose period 1, high dose period 1 and Period 2 therefore the numbers in the milestones individually do not add up to number started.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Participants in each of the three arms (Light Weight: <25 kg , Middle Weight: 25 kg to <40 kg and Heavy Weight: ≥40 kg) received different doses of drug during Low dose period 1, high dose period 1 and Period 2 therefore the numbers in the milestones individually do not add up to number

started.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Participants in each of the three arms (Light Weight: <25 kg , Middle Weight: 25 kg to <40 kg and Heavy Weight: ≥40 kg) received different doses of drug during Low dose period 1, high dose period 1 and Period 2 therefore the numbers in the milestones individually do not add up to number started.

[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Participants in each of the three arms (Light Weight: <25 kg , Middle Weight: 25 kg to <40 kg and Heavy Weight: ≥40 kg) received different doses of drug during Low dose period 1, high dose period 1 and Period 2 therefore the numbers in the milestones individually do not add up to number started.

[6] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Participants in each of the three arms (Light Weight: <25 kg , Middle Weight: 25 kg to <40 kg and Heavy Weight: ≥40 kg) received different doses of drug during Low dose period 1, high dose period 1 and Period 2 therefore the numbers in the milestones individually do not add up to number started.

[7] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Participants in each of the three arms (Light Weight: <25 kg , Middle Weight: 25 kg to <40 kg and Heavy Weight: ≥40 kg) received different doses of drug during Low dose period 1, high dose period 1 and Period 2 therefore the numbers in the milestones individually do not add up to number started.

[8] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Participants in each of the three arms (Light Weight: <25 kg , Middle Weight: 25 kg to <40 kg and Heavy Weight: ≥40 kg) received different doses of drug during Low dose period 1, high dose period 1 and Period 2 therefore the numbers in the milestones individually do not add up to number started.

[9] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Participants in each of the three arms (Light Weight: <25 kg , Middle Weight: 25 kg to <40 kg and Heavy Weight: ≥40 kg) received different doses of drug during Low dose period 1, high dose period 1 and Period 2 therefore the numbers in the milestones individually do not add up to number started.

[10] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Participants in each of the three arms (Light Weight: <25 kg , Middle Weight: 25 kg to <40 kg and Heavy Weight: ≥40 kg) received different doses of drug during Low dose period 1, high dose period 1 and Period 2 therefore the numbers in the milestones individually do not add up to number started.

[11] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Participants in each of the three arms (Light Weight: <25 kg , Middle Weight: 25 kg to <40 kg and Heavy Weight: ≥40 kg) received different doses of drug during Low dose period 1, high dose period 1 and Period 2 therefore the numbers in the milestones individually do not add up to number started.

[12] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Participants in each of the three arms (Light Weight: <25 kg , Middle Weight: 25 kg to <40 kg and Heavy Weight: ≥40 kg) received different doses of drug during Low dose period 1, high dose period 1 and Period 2 therefore the numbers in the milestones individually do not add up to number started.

[13] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Participants in each of the three arms (Light Weight: <25 kg , Middle Weight: 25 kg to <40

kg and Heavy Weight: ≥40 kg) received different doses of drug during Low dose period 1, high dose period 1 and Period 2 therefore the numbers in the milestones individually do not add up to number started.
[14] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Participants in each of the three arms (Light Weight: <25 kg , Middle Weight: 25 kg to <40 kg and Heavy Weight: ≥40 kg) received different doses of drug during Low dose period 1, high dose period 1 and Period 2 therefore the numbers in the milestones individually do not add up to number started.
[15] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Participants in each of the three arms (Light Weight: <25 kg , Middle Weight: 25 kg to <40 kg and Heavy Weight: ≥40 kg) received different doses of drug during Low dose period 1, high dose period 1 and Period 2 therefore the numbers in the milestones individually do not add up to number started.
[16] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Participants in each of the three arms (Light Weight: <25 kg , Middle Weight: 25 kg to <40 kg and Heavy Weight: ≥40 kg) received different doses of drug during Low dose period 1, high dose period 1 and Period 2 therefore the numbers in the milestones individually do not add up to number started.
[17] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Participants in each of the three arms (Light Weight: <25 kg , Middle Weight: 25 kg to <40 kg and Heavy Weight: ≥40 kg) received different doses of drug during Low dose period 1, high dose period 1 and Period 2 therefore the numbers in the milestones individually do not add up to number started.
[18] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Participants in each of the three arms (Light Weight: <25 kg , Middle Weight: 25 kg to <40 kg and Heavy Weight: ≥40 kg) received different doses of drug during Low dose period 1, high dose period 1 and Period 2 therefore the numbers in the milestones individually do not add up to number started.
[19] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Participants in each of the three arms (Light Weight: <25 kg , Middle Weight: 25 kg to <40 kg and Heavy Weight: ≥40 kg) received different doses of drug during Low dose period 1, high dose period 1 and Period 2 therefore the numbers in the milestones individually do not add up to number started.
[20] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Participants in each of the three arms (Light Weight: <25 kg , Middle Weight: 25 kg to <40 kg and Heavy Weight: ≥40 kg) received different doses of drug during Low dose period 1, high dose period 1 and Period 2 therefore the numbers in the milestones individually do not add up to number started.
[21] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Participants in each of the three arms (Light Weight: <25 kg , Middle Weight: 25 kg to <40 kg and Heavy Weight: ≥40 kg) received different doses of drug during Low dose period 1, high dose period 1 and Period 2 therefore the numbers in the milestones individually do not add up to number started.
[22] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Participants in each of the three arms (Light Weight: <25 kg , Middle Weight: 25 kg to <40 kg and Heavy Weight: ≥40 kg) received different doses of drug during Low dose period 1, high dose period 1 and Period 2 therefore the numbers in the milestones individually do not add up to number started.
[23] - The number of subjects at this milestone seems inconsistent with the number of subjects in the

arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Participants in each of the three arms (Light Weight: <25 kg , Middle Weight: 25 kg to <40 kg and Heavy Weight: ≥40 kg) received different doses of drug during Low dose period 1, high dose period 1 and Period 2 therefore the numbers in the milestones individually do not add up to number started.
[24] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Participants in each of the three arms (Light Weight: <25 kg , Middle Weight: 25 kg to <40 kg and Heavy Weight: ≥40 kg) received different doses of drug during Low dose period 1, high dose period 1 and Period 2 therefore the numbers in the milestones individually do not add up to number started.
[25] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Participants in each of the three arms (Light Weight: <25 kg , Middle Weight: 25 kg to <40 kg and Heavy Weight: ≥40 kg) received different doses of drug during Low dose period 1, high dose period 1 and Period 2 therefore the numbers in the milestones individually do not add up to number started.

Period 2

Period 2 title	Period 2
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Light Weight: <25 kg

Arm description:

Period 2: Open Label Extension for 2 years.

7 mg, 8 mg, 15 mg or 20 mg tadalafil administered once daily (QD) in oral suspension formulation.

Arm type	Experimental
Investigational medicinal product name	Tadalafil
Investigational medicinal product code	
Other name	LY450190
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

Period 2: Open Label Extension for 2 years.

7 mg, 8 mg, 15 mg or 20 mg tadalafil administered once daily (QD) in oral suspension formulation.

Arm title	Middle Weight: 25 kg to <40 kg

Arm description:

Period 2: Open Label Extension for 2 years.

7.5 mg, 10 mg, 15 mg or 20 mg tadalafil administered once daily (QD) in oral tablet.

Arm type	Experimental
Investigational medicinal product name	Tadalafil
Investigational medicinal product code	
Other name	LY450190
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Period 2: Open Label Extension for 2 years.

7.5 mg, 10 mg, 15 mg or 20 mg tadalafil administered once daily (QD) in oral tablet.

Arm title	Heavy Weight: ≥40 kg

Arm description:

Period 2: Open Label Extension for 2 years.

15 mg, 20 mg or 40 mg tadalafil administered once daily (QD) in oral tablet.

Arm type	Experimental
Investigational medicinal product name	Tadalafil
Investigational medicinal product code	
Other name	LY450190
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Period 2: Open Label Extension for 2 years.

15 mg, 20 mg or 40 mg tadalafil administered once daily (QD) in oral tablet.

Number of subjects in period 2	Light Weight: <25 kg	Middle Weight: 25 kg to <40 kg	Heavy Weight: ≥40 kg
Started	6	6	6
Received 7 mg	1 [26]	0 [27]	0 [28]
Received 7.5 mg	0 [29]	2 [30]	0 [31]
Received 8 mg	1 [32]	0 [33]	0 [34]
Received 10 mg	0 [35]	1 [36]	0 [37]
Received 15 mg	1 [38]	2 [39]	1 [40]
Received 20 mg	3 [41]	1 [42]	4
Receceived 40 mg	0 [43]	0 [44]	1 [45]
Completed	5	5	4
Not completed	1	1	2
Physician decision	-	-	1
Non-Compliance with Study Drug	1	-	-
Death	-	1	1

Notes:

[26] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Participants in each of the three arms (Light Weight: <25 kg , Middle Weight: 25 kg to <40 kg and Heavy Weight: ≥40 kg) received different doses of drug during Low dose period 1, high dose period 1 and Period 2 therefore the numbers in the milestones individually do not add up to number started.

[27] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Participants in each of the three arms (Light Weight: <25 kg , Middle Weight: 25 kg to <40 kg and Heavy Weight: ≥40 kg) received different doses of drug during Low dose period 1, high dose period 1 and Period 2 therefore the numbers in the milestones individually do not add up to number started.

[28] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Participants in each of the three arms (Light Weight: <25 kg , Middle Weight: 25 kg to <40

kg and Heavy Weight: ≥40 kg) received different doses of drug during Low dose period 1, high dose period 1 and Period 2 therefore the numbers in the milestones individually do not add up to number started.
[29] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Participants in each of the three arms (Light Weight: <25 kg , Middle Weight: 25 kg to <40 kg and Heavy Weight: ≥40 kg) received different doses of drug during Low dose period 1, high dose period 1 and Period 2 therefore the numbers in the milestones individually do not add up to number started.
[30] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Participants in each of the three arms (Light Weight: <25 kg , Middle Weight: 25 kg to <40 kg and Heavy Weight: ≥40 kg) received different doses of drug during Low dose period 1, high dose period 1 and Period 2 therefore the numbers in the milestones individually do not add up to number started.
[31] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Participants in each of the three arms (Light Weight: <25 kg , Middle Weight: 25 kg to <40 kg and Heavy Weight: ≥40 kg) received different doses of drug during Low dose period 1, high dose period 1 and Period 2 therefore the numbers in the milestones individually do not add up to number started.
[32] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Participants in each of the three arms (Light Weight: <25 kg , Middle Weight: 25 kg to <40 kg and Heavy Weight: ≥40 kg) received different doses of drug during Low dose period 1, high dose period 1 and Period 2 therefore the numbers in the milestones individually do not add up to number started.
[33] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Participants in each of the three arms (Light Weight: <25 kg , Middle Weight: 25 kg to <40 kg and Heavy Weight: ≥40 kg) received different doses of drug during Low dose period 1, high dose period 1 and Period 2 therefore the numbers in the milestones individually do not add up to number started.
[34] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Participants in each of the three arms (Light Weight: <25 kg , Middle Weight: 25 kg to <40 kg and Heavy Weight: ≥40 kg) received different doses of drug during Low dose period 1, high dose period 1 and Period 2 therefore the numbers in the milestones individually do not add up to number started.
[35] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Participants in each of the three arms (Light Weight: <25 kg , Middle Weight: 25 kg to <40 kg and Heavy Weight: ≥40 kg) received different doses of drug during Low dose period 1, high dose period 1 and Period 2 therefore the numbers in the milestones individually do not add up to number started.
[36] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Participants in each of the three arms (Light Weight: <25 kg , Middle Weight: 25 kg to <40 kg and Heavy Weight: ≥40 kg) received different doses of drug during Low dose period 1, high dose period 1 and Period 2 therefore the numbers in the milestones individually do not add up to number started.
[37] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Participants in each of the three arms (Light Weight: <25 kg , Middle Weight: 25 kg to <40 kg and Heavy Weight: ≥40 kg) received different doses of drug during Low dose period 1, high dose period 1 and Period 2 therefore the numbers in the milestones individually do not add up to number started.
[38] - The number of subjects at this milestone seems inconsistent with the number of subjects in the

arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Participants in each of the three arms (Light Weight: <25 kg , Middle Weight: 25 kg to <40 kg and Heavy Weight: ≥40 kg) received different doses of drug during Low dose period 1, high dose period 1 and Period 2 therefore the numbers in the milestones individually do not add up to number started.
[39] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Participants in each of the three arms (Light Weight: <25 kg , Middle Weight: 25 kg to <40 kg and Heavy Weight: ≥40 kg) received different doses of drug during Low dose period 1, high dose period 1 and Period 2 therefore the numbers in the milestones individually do not add up to number started.
[40] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Participants in each of the three arms (Light Weight: <25 kg , Middle Weight: 25 kg to <40 kg and Heavy Weight: ≥40 kg) received different doses of drug during Low dose period 1, high dose period 1 and Period 2 therefore the numbers in the milestones individually do not add up to number started.
[41] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Participants in each of the three arms (Light Weight: <25 kg , Middle Weight: 25 kg to <40 kg and Heavy Weight: ≥40 kg) received different doses of drug during Low dose period 1, high dose period 1 and Period 2 therefore the numbers in the milestones individually do not add up to number started.
[42] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Participants in each of the three arms (Light Weight: <25 kg , Middle Weight: 25 kg to <40 kg and Heavy Weight: ≥40 kg) received different doses of drug during Low dose period 1, high dose period 1 and Period 2 therefore the numbers in the milestones individually do not add up to number started.
[43] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Participants in each of the three arms (Light Weight: <25 kg , Middle Weight: 25 kg to <40 kg and Heavy Weight: ≥40 kg) received different doses of drug during Low dose period 1, high dose period 1 and Period 2 therefore the numbers in the milestones individually do not add up to number started.
[44] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Participants in each of the three arms (Light Weight: <25 kg , Middle Weight: 25 kg to <40 kg and Heavy Weight: ≥40 kg) received different doses of drug during Low dose period 1, high dose period 1 and Period 2 therefore the numbers in the milestones individually do not add up to number started.
[45] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Participants in each of the three arms (Light Weight: <25 kg , Middle Weight: 25 kg to <40 kg and Heavy Weight: ≥40 kg) received different doses of drug during Low dose period 1, high dose period 1 and Period 2 therefore the numbers in the milestones individually do not add up to number started.

Baseline characteristics

Reporting groups	
Reporting group title	Light Weight: <25 kg

Reporting group description:

Period 1: 2 milligram (mg) or 4 mg tadalafil administered once daily (QD) in oral suspension formulation for 5 weeks then 8 mg,10 mg,15 mg or 20 mg tadalafil was administered QD in oral suspension formulation for 5 weeks.

Reporting group title	Middle Weight: 25 kg to <40 kg

Reporting group description:

Period 1: 5 mg tadalafil tablet administered QD for 5 weeks then 10 mg, 15 mg or 20 mg tablet tadalafil administered QD for 5 weeks.

Reporting group title	Heavy Weight: ≥40 kg

Reporting group description:

Period 1: 10 mg tadalafil tablet administered QD for 5 weeks then 20 mg or 40 mg tablet tadalafil administered QD for 5 weeks.

Reporting group values	Light Weight: <25 kg	Middle Weight: 25 kg to <40 kg	Heavy Weight: ≥40 kg
Number of subjects	6	7	6
Age categorical Units: Subjects			
Age continuous			
Participants who received at least one dose of study drug. Participants were first administered a low dose to explore PK of tadalafil and determine a high dose within the weight cohort. Per protocol, the summary was based on weight cohorts.			
Units: years			
arithmetic mean	5.00	10.91	14.45
full range (min-max)	2.5 to 8.0	7.3 to 17.9	11.3 to 17.6
Gender categorical Units: Subjects			
Female	4	5	4
Male	2	2	2
Race Units: Subjects			
American Indian or Alaska Native	1	0	0
Asian	0	2	1
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	0	0
White	4	5	5
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Region of Enrollment Units: Subjects			
Canada	3	1	1

United States	1	0	1
Poland	1	2	2
United Kingdom	0	3	0
France	0	1	1
Spain	1	0	1

Reporting group values	Total		
Number of subjects	19		
Age categorical Units: Subjects			

Age continuous			
Participants who received at least one dose of study drug. Participants were first administered a low dose to explore PK of tadalafil and determine a high dose within the weight cohort. Per protocol, the summary was based on weight cohorts.			
Units: years arithmetic mean full range (min-max)	--		
Gender categorical Units: Subjects			
Female	13		
Male	6		
Race Units: Subjects			
American Indian or Alaska Native	1		
Asian	3		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	1		
White	14		
More than one race	0		
Unknown or Not Reported	0		
Region of Enrollment Units: Subjects			
Canada	5		
United States	2		
Poland	5		
United Kingdom	3		
France	2		
Spain	2		

End points

End points reporting groups

Reporting group title	Light Weight: <25 kg

Reporting group description:

Period 1: 2 milligram (mg) or 4 mg tadalafil administered once daily (QD) in oral suspension formulation for 5 weeks then 8 mg,10 mg,15 mg or 20 mg tadalafil was administered QD in oral suspension formulation for 5 weeks.

Reporting group title	Middle Weight: 25 kg to <40 kg

Reporting group description:

Period 1: 5 mg tadalafil tablet administered QD for 5 weeks then 10 mg, 15 mg or 20 mg tablet tadalafil administered QD for 5 weeks.

Reporting group title	Heavy Weight: ≥40 kg

Reporting group description:

Period 1: 10 mg tadalafil tablet administered QD for 5 weeks then 20 mg or 40 mg tablet tadalafil administered QD for 5 weeks.

Reporting group title	Light Weight: <25 kg

Reporting group description:

Period 2: Open Label Extension for 2 years.

7 mg, 8 mg, 15 mg or 20 mg tadalafil administered once daily (QD) in oral suspension formulation.

Reporting group title	Middle Weight: 25 kg to <40 kg

Reporting group description:

Period 2: Open Label Extension for 2 years.

7.5 mg, 10 mg, 15 mg or 20 mg tadalafil administered once daily (QD) in oral tablet.

Reporting group title	Heavy Weight: ≥40 kg

Reporting group description:

Period 2: Open Label Extension for 2 years.

15 mg, 20 mg or 40 mg tadalafil administered once daily (QD) in oral tablet.

Primary: Population Pharmacokinetics: Area Under the Concentration Curve Versus Time at a Dosing Interval at Steady State (AUCtau) for Tadalafil

End point title	Population Pharmacokinetics: Area Under the Concentration Curve Versus Time at a Dosing Interval at Steady State (AUCtau) for Tadalafil[1]

End point description:

Population Pharmacokinetics: Area Under the Concentration Curve Versus Time at a Dosing Interval at Steady State (AUCtau) for Tadalafil .

Analysis Population Description: All participants who received at least one dose of study drug and had evaluable PK data including all dose levels on Day 1, 14 and 49. Per protocol, the summary reflects potential exposure of the high dose within each weight cohort

End point type	Primary

End point timeframe:

Period 1: Pre Dose and 2, 4, 8, 12, and 24 Hours Post Dose on Days 1, 14 and 49; with single dose measures on Day 1 and steady-state measurements on Days 14 and 49.

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: Per protocol, statistical analysis were not planned for this outcome measure.

End point values	Light Weight: <25 kg	Middle Weight: 25 kg to <40 kg	Heavy Weight: ≥40 kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	7	6	
Units: nanograms* hour per milliliter(ng*hr/mL)				
median (confidence interval 90%)				
Not Taking Bosentan	8170 (3850 to 16700)	8390 (4130 to 18400)	15200 (6980 to 31100)	
Taking Concomitant Bosentan	4550 (2170 to 9450)	5000 (2440 to 10600)	8990 (4270 to 19500)	

Statistical analyses

No statistical analyses for this end point

Primary: Population Pharmacokinetics: Average Concentration (Cmean,ss) of for Tadalafil at Steady-State

End point title	Population Pharmacokinetics: Average Concentration (Cmean,ss) of for Tadalafil at Steady-State[2]

End point description:

Population Pharmacokinetics: Average Concentration (Cmean,ss) of for Tadalafil at Steady-State.

Analysis Population Description: All participants who received at least one dose of study drug and had evaluable PK data including all dose levels on Day 1, 14 and 49. Per protocol, the summary reflects potential exposure of the high dose within each weight cohort.

End point type	Primary

End point timeframe:

Period 1: Pre Dose and 2, 4, 8, 12, and 24 Hours Post Dose on Days 1, 14 and 49; with single dose measures on Day 1 and steady-state measurements on Days 14 and 49.

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: Per protocol, statistical analysis were not planned for this outcome measure.

End point values	Light Weight: <25 kg	Middle Weight: 25 kg to <40 kg	Heavy Weight: ≥40 kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	7	6	
Units: nanograms per milliliter (ng/mL)				
median (confidence interval 90%)				
Not Taking Bosentan	340 (161 to 694)	350 (172 to 767)	633 (291 to 1300)	
Taking Concomitant Bosentan	190 (90.4 to 394)	209 (102 to 440)	375 (178 to 815)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Clinical Worsening

End point title	Percentage of Participants With Clinical Worsening

End point description:

Clinical worsening was defined as any of the following: death, lung or heart transplantation, atrial septostomy or Potts' shunt, hospitalization for Pulmonary Arterial Hypertension (PAH) progression, new onset syncope, initiation of new PAH therapy, or increase of 1 or more in World Health Organization(WHO) Functional Class (except for participants already in Class IV; only for participants unable to perform the 6 minute walk (6MW) test; worsening of WHO functional class by 1 or more for participants who can perform a 6 minute walk (6MW) test and who have a decrease of ≥ 20% in the 6 minute walk distance (for those participants who are ≥6 years of age) and an increase in the dose of endothelin receptor agonist (ERA) medication.

Analysis Population Description: All participants who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

Baseline Up to 27 Months

End point values	Light Weight: <25 kg	Middle Weight: 25 kg to <40 kg	Heavy Weight: ≥40 kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	7	6	
Units: percentage of participants				
number (not applicable)	50.00	28.57	33.33	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Palatability of the Tadalafil Suspension

End point title	Number of Participants With Palatability of the Tadalafil Suspension[3]

End point description:

The Taste Assessment Questionnaire (TAQ) questions were:

TAQRES1: Please rate the bitterness level. TAQRES2: Please rate the sweetness level. TAQRES3: Please rate the aftertaste. TAQRES4: Please rate the overall acceptability of the taste for daily use.

Analysis Population Description: Participants who received at least one oral suspension dose of study drug in the Light-weight cohort (≥2 years of age). Per protocol, palatability of the tadalafil suspension was evaluated in the Light-weight cohort only.

End point type	Secondary

End point timeframe:

Day 35 (high dose)

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Per protocol, only participants in Light Weight: <25 kg were analyzed for this outcome measure.

End point values	Light Weight: <25 kg			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: Count of Participants				
TAQRES1: Extremely bitter	0			
TAQRES1: Very bitter	0			
TAQRES1: Moderately bitter	0			
TAQRES1: Slightly bitter	0			
TAQRES1: Not bitter	3			
TAQRES2: Extremely sweet	1			
TAQRES2: Very sweet	0			
TAQRES2: Moderately sweet	1			
TAQRES2: Slightly sweet	1			
TAQRES2: Not sweet	0			
TAQRES3: Extreme aftertaste	0			
TAQRES3: Strong aftertaste	1			
TAQRES3: Moderate aftertaste	0			
TAQRES3:Slight aftertaste	0			
TAQRES3:No aftertaste	2			
TAQRES4: Not acceptable	0			
TAQRES4: Slightly acceptable	0			
TAQRES4: Acceptable	2			
TAQRES4: Very acceptable	1			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up To 27 Months

Adverse event reporting additional description:

All participants who received at least one dose of study drug. Participants were first administered a low dose to explore PK of tadalafil and determine a high dose within the weight cohort. Per protocol, the summary was based on weight cohorts.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Light Weight Cohort

Reporting group description:

Period 1: 2 milligram (mg) or 4 mg tadalafil administered once daily (QD) in oral suspension formulation for 5 weeks then 8 mg,10 mg,15 mg or 20 mg tadalafil was administered QD in oral suspension formulation for 5 weeks.

Period 2: Open Label Extension for 2 years.

7 mg, 8 mg, 15 mg or 20 mg tadalafil administered once daily (QD) in oral suspension formulation.

Reporting group title	Middle Weight Cohort

Reporting group description:

Period 1: 5 mg tadalafil tablet administered QD for 5 weeks then 10 mg, 15 mg or 20 mg tablet tadalafil administered QD for 5 weeks.

Period 2: Open Label Extension for 2 years.

7.5 mg, 10 mg, 15 mg or 20 mg tadalafil administered once daily (QD) in oral tablet.

Reporting group title	Heavy Weight Cohort

Reporting group description:

Period 1: 10 mg tadalafil tablet administered QD for 5 weeks then 20 mg or 40 mg tablet tadalafil administered QD for 5 weeks.

Period 2: Open Label Extension for 2 years.

15 mg, 20 mg or 40 mg tadalafil administered once daily (QD) in oral tablet.

Serious adverse events	Light Weight Cohort	Middle Weight Cohort	Heavy Weight Cohort
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 6 (16.67%)	4 / 7 (57.14%)	3 / 6 (50.00%)
number of deaths (all causes)	0	1	1
number of deaths resulting from adverse events	0	0	0
Cardiac disorders			
cardiac failure			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Nervous system disorders			
febrile convulsion			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
presyncope			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
seizure			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
syncope			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
pyrexia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
gastritis			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
ovarian cyst			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed[1]	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
pulmonary arterial hypertension			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 6 (16.67%)	1 / 7 (14.29%)	2 / 6 (33.33%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Infections and infestations			
pneumonia viral			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
viral infection			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
type 1 diabetes mellitus			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Gender specific event

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

Non-serious adverse events	Light Weight Cohort	Middle Weight Cohort	Heavy Weight Cohort
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)	7 / 7 (100.00%)	6 / 6 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
skin papilloma			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Vascular disorders			
flushing			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
haematoma			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
hypertension			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
orthostatic hypotension			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
vasodilatation			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			

catheter site pain			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
chest discomfort			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
disease progression			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
face oedema			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
puncture site pain			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	4
pyrexia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	2 / 6 (33.33%)	1 / 7 (14.29%)	1 / 6 (16.67%)
occurrences (all)	7	1	1
thirst			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Immune system disorders			
allergy to arthropod sting			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			

dysmenorrhoea			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed[2]	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
menorrhagia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed[3]	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
ovarian cyst			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed[4]	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
bronchospasm			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	3
catarrh			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	2
cough			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	1 / 6 (16.67%)
occurrences (all)	0	2	1
dyspnoea			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
epistaxis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 6 (16.67%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
oropharyngeal pain			
alternative dictionary used:			

MedDRA 21.1			
subjects affected / exposed	0 / 6 (0.00%)	3 / 7 (42.86%)	0 / 6 (0.00%)
occurrences (all)	0	3	0
productive cough			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
pulmonary arterial hypertension			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
rhinitis allergic			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
rhinorrhoea			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	2 / 6 (33.33%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	2	0	1
Psychiatric disorders			
abnormal behaviour			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
agitation			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
anxiety			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Investigations			
cytogenetic analysis abnormal			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
electrocardiogram qt prolonged			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
exercise test abnormal			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
oxygen saturation decreased			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
serum ferritin decreased			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
arthropod bite			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
radius fracture			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Congenital, familial and genetic disorders			
dermoid cyst			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			

angina pectoris			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	2 / 6 (33.33%)
occurrences (all)	1	0	2
cyanosis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
palpitations			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
disturbance in attention			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
dizziness			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
dizziness postural			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
headache			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	2 / 6 (33.33%)	2 / 7 (28.57%)	2 / 6 (33.33%)
occurrences (all)	2	2	2
lethargy			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	2
migraine			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
syncope			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
tension headache			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	2
Blood and lymphatic system disorders			
iron deficiency anaemia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Ear and labyrinth disorders			
ear pain			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	2
Eye disorders			
eye pain			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
hypermetropia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
swelling of eyelid			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
vision blurred			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
abdominal distension			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
abdominal pain			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 6 (16.67%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	3	1	0
abdominal pain upper			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
anal fissure			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
constipation			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
diarrhoea			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
faeces soft			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
gastrooesophageal reflux disease			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	1 / 6 (16.67%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
haematochezia			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
nausea			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 6 (16.67%)	1 / 7 (14.29%)	1 / 6 (16.67%)
occurrences (all)	1	1	1
toothache			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	2
vomiting			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	2 / 6 (33.33%)	2 / 7 (28.57%)	1 / 6 (16.67%)
occurrences (all)	2	2	1
Skin and subcutaneous tissue disorders			
dermatitis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
dry skin			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
ecchymosis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	2 / 6 (33.33%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
hyperkeratosis			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
petechiae			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
pruritus			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
rash			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 6 (16.67%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	4	1	0
swelling face			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
urticaria			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 6 (0.00%)	2 / 7 (28.57%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Musculoskeletal and connective tissue disorders			
musculoskeletal chest pain			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
pain in extremity			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 6 (0.00%)	2 / 7 (28.57%)	1 / 6 (16.67%)
occurrences (all)	0	3	1
pain in jaw			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Infections and infestations			
bronchitis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	2 / 6 (33.33%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	2	1	0
ear infection			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 6 (16.67%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	1	3	0
gastroenteritis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	3 / 6 (50.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	4	0	1
gastrointestinal infection			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	2
influenza			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
laryngitis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
nasopharyngitis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	2 / 6 (33.33%)	1 / 7 (14.29%)	2 / 6 (33.33%)
occurrences (all)	5	1	7
otitis media acute			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
pharyngitis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
respiratory tract infection			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	5
respiratory tract infection viral			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
sinusitis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
toxoplasmosis			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
upper respiratory tract infection			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	2
urinary tract infection			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
viral infection			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0

viral upper respiratory tract infection alternative dictionary used: MedDRA 21.1 subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 7 (14.29%) 1	0 / 6 (0.00%) 0
Metabolism and nutrition disorders decreased appetite alternative dictionary used: MedDRA 21.1 subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	1 / 7 (14.29%) 1	0 / 6 (0.00%) 0

Notes:

[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: Gender specific event

[3] - 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: Gender specific event

[4] - 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: Gender specific event

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 April 2012	Amendment b: Substantial due to significant changes to the Inclusion/Exclusion Criteria.
09 August 2015	Amendment d: Revised tadalafil risk profile with a safety consideration of newly approved guanylate cyclase stimulator under the section of interaction of tadalafil with other drugs. Other changes with Inclusion/Exclusion criteria.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported