

**Clinical trial results:****A Double-Blind Efficacy and Safety Study of the Phosphodiesterase Type 5 Inhibitor Tadalafil in Pediatric Patients with Pulmonary Arterial Hypertension****Summary**

EudraCT number	2012-002354-23
Trial protocol	GB DE BE IT AT NL PL ES RO FR
Global end of trial date	

Results information

Result version number	v1
This version publication date	22 March 2020
First version publication date	22 March 2020

Trial information**Trial identification**

Sponsor protocol code	H6D-MC-LVHV
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01824290
WHO universal trial number (UTN)	-
Other trial identifiers	Trial Number: 10609

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)	EMA-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?	No

Notes:

Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	18 March 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 March 2019
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

The main purpose of this study is to evaluate the safety and efficacy of tadalafil in pediatric participants with pulmonary arterial hypertension. Participants will receive study treatment for 6 months in the double-blind period (Period 1), and then will be eligible to enroll into an open-label 2 year extension period (Period 2) during which participants will receive tadalafil.

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	05 February 2014
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	Japan: 2
Country: Number of subjects enrolled	Turkey: 3
Country: Number of subjects enrolled	Brazil: 15
Country: Number of subjects enrolled	Mexico: 5
Country: Number of subjects enrolled	Israel: 6
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Poland: 1
Worldwide total number of subjects	35
EEA total number of subjects	4

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)	22
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

No Text Available

Pre-assignment

Screening details:

Per protocol and statistical analysis plan (SAP), the primary and secondary analysis from period 1 were performed to compare all tadalafil participants together versus all placebo participants together. Period 2 data will be reported after study completion.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Period 1: Participants received placebo orally by tablets once a day.

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

Dosage and administration details:

Participants received placebo orally by tablets once a day.

Arm title	Tadalafil
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Arm description:

Period 1: 20 mg middle weight cohort or 40 mg for heavy weight cohort administered orally by tablets once a day.

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:

20 mg middle weight cohort or 40 mg for heavy weight cohort administered orally by tablets once a day.

Number of subjects in period 1	Placebo	Tadalafil
Started	18	17
Received at least one dose of study drug	18	17
Received 20 mg	0 ^[1]	4 ^[2]
Received 40 mg	0 ^[3]	13 ^[4]
Completed	15	15
Not completed	3	2
Parent/Caregiver Decision	1	1
Investigator Reported Clinical Worsening	1	1
Entry Criteria Not Met	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: This milestone represents tadalafil arm only.

[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: The milestone represents how many participants received 20 mg tadalafil.

[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: This milestone represents tadalafil arm only.

[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: The milestone represents how many participants received 40 mg tadalafil.

Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description:	
Period 1: Participants received placebo orally by tablets once a day.	
Reporting group title	Tadalafil
Reporting group description:	
Period 1: 20 mg middle weight cohort or 40 mg for heavy weight cohort administered orally by tablets once a day.	

Reporting group values	Placebo	Tadalafil	Total
Number of subjects	18	17	35
Age categorical			
Units: Subjects			
Age continuous			
All participants who received at least one dose. Per protocol and statistical analysis plan (SAP), the primary and secondary analysis were performed to compare all tadalafil participants together versus all placebo participants together.			
Units: years			
arithmetic mean	12.8	14.1	
standard deviation	± 3.39	± 3.49	-
Gender categorical			
Units: Subjects			
Female	9	10	19
Male	9	7	16
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	7	8	15
Not Hispanic or Latino	6	4	10
Unknown or Not Reported	5	5	10
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	1	3	4
Asian	1	1	2
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	2	1	3
White	14	12	26
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Region of Enrollment			
Units: Subjects			
Japan	1	1	2
Turkey	2	1	3
Brazil	9	6	15
Mexico	1	4	5
Israel	2	4	6
France	1	1	2

Germany	1	0	1
Poland	1	0	1

6 Minute Walk Distance			
Units: Meters			
arithmetic mean	476.7	485.8	
standard deviation	± 105.11	± 160.231	-

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Period 1: Participants received placebo orally by tablets once a day.	
Reporting group title	Tadalafil
Reporting group description:	
Period 1: 20 mg middle weight cohort or 40 mg for heavy weight cohort administered orally by tablets once a day.	
Subject analysis set title	20 mg Tadalafil
Subject analysis set type	Per protocol
Subject analysis set description:	
Period 1: 20 mg tadalafil administered orally by tablets once a day with concomitant endothelin receptor antagonist (ERA).	
Subject analysis set title	40 mg Tadalafil
Subject analysis set type	Per protocol
Subject analysis set description:	
Period 1: 40 mg tadalafil administered orally by tablets once a day with concomitant endothelin receptor antagonist (ERA).	

Primary: Period 1: Change from Baseline to Week 24 in a 6 Minute Walk (MW) Distance in Meters

End point title	Period 1: Change from Baseline to Week 24 in a 6 Minute Walk (MW) Distance in Meters
End point description:	
6MWD in meters assessed in a subset of participants who are ≥ 6 to < 18 years of age who are developmentally capable of performing a 6MW test. Change from baseline was derived using mixed model repeated measures (MMRM) with terms for treatment group, visit, baseline 6MWD, and treatment-by-visit interaction.	
Analysis Population Description: All participants who received at least one dose of study drug who were $> = 6$ to < 18 years of age and were capable of performing a 6MW test.	
End point type	Primary
End point timeframe:	
Baseline, Week 24	

End point values	Placebo	Tadalafil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: Meters				
least squares mean (standard error)	36.60 (\pm 20.776)	60.48 (\pm 20.410)		

Statistical analyses

Statistical analysis title	6 Minute Walk (MW) Distance in Meters
Comparison groups	Placebo v Tadalafil

Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	23.88
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-14.25
upper limit	62

Secondary: Period 1: Time to Adjudicated Clinical Worsening (CW)

End point title	Period 1: Time to Adjudicated Clinical Worsening (CW)
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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 (including increase in the dose of existing PAH specific concomitant therapy, such as endothelin receptor agonist or beraprost medication), 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 $\geq 20\%$ in the 6 minute walk distance (for those participants who are ≥ 6 years of age). Criteria for CW (from Period 1) were adjudicated by an independent, blinded study-specific Clinical Endpoint Committee (CEC). This adjudication was used for data analysis, and was not used to guide

End point type	Secondary
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End point timeframe:

Baseline through Week 24

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

End point values	Placebo	Tadalafil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18 ^[1]	17 ^[2]		
Units: Weeks				
median (confidence interval 95%)	9999 (9999 to 9999)	9999 (9999 to 9999)		

Notes:

[1] - 9999=Data Not Available (NA). There was no confirmed adjudicated CW case to report.

[2] - 9999=Data Not Available (NA). There was no confirmed adjudicated CW case to report.

Statistical analyses

No statistical analyses for this end point

Secondary: Period 1: Percentage of Participants Who Experience CW

End point title	Period 1: Percentage of Participants Who Experience CW
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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 (including increase in the dose of existing PAH specific

concomitant therapy, such as endothelin receptor agonist or beraprost medication), 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 $\geq 20\%$ in the 6 minute walk distance (for those participants who are ≥ 6 years of age). Criteria for CW (from Period 1) were adjudicated by an independent, blinded study-specific Clinical Endpoint Committee (CEC). This adjudication was used for data analysis, and was not used to guide subject

End point type	Secondary
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End point timeframe:

Baseline through Week 24

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

End point values	Placebo	Tadalafil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	17		
Units: percentage of participants				
number (not applicable)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Period 1: Pharmacokinetics (PK): Apparent Clearance (CL/F) of tadalafil

End point title	Period 1: Pharmacokinetics (PK): Apparent Clearance (CL/F) of tadalafil
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End point description:

Period 1: Pharmacokinetics (PK): Apparent Clearance (CL/F) of Tadalafil at Steady-state.

Analysis Population Description: All participants who received at least one dose of study drug and had evaluable PK data.

9999= NA.

For 20 mg tadalafil with concomitant bosentan, n=3.

For 20 mg tadalafil no bosentan (ERA: macitentan), n = 1. For n = 1, geometric mean and geometric coefficient of variation could not be calculated. Individual value is 2.68.

For 40 mg tadalafil No bosentan (ERA: Macitentan), n=0.

End point type	Secondary
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End point timeframe:

Week 2, Week 4, Week 16 and Week 24

End point values	20 mg Tadalafil	40 mg Tadalafil		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4 ^[3]	13 ^[4]		
Units: Liter Per Hour (L/hr)				
geometric mean (geometric coefficient of variation)				
With concomitant bosentan	3.63 (\pm 38.1)	4.49 (\pm 28.2)		

No bosentan (ERA: Macitentan)	9999 (\pm 9999)	9999 (\pm 9999)		
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Notes:

[3] - 9999= NA.

For 20 mg tadalafil No bosentan (ERA: Macitentan), n = 1.

[4] - 9999= NA.

For 40 mg tadalafil No bosentan (ERA: Macitentan), n=0.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Period 1: Up To 24 Weeks

Adverse event reporting additional description:

All participants who received at least one dose of study drug. Period 2 data will be reported at study completion.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.1
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Reporting groups

Reporting group title	Tadalafil
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Reporting group description:

Period 1: 20 mg or 40 mg administered orally by tablets once a day.

Reporting group title	Placebo
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Reporting group description:

Period 1: Participants received placebo orally by tablets once a day.

Serious adverse events	Tadalafil	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Tadalafil	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 17 (88.24%)	8 / 18 (44.44%)	
Vascular disorders			
flushing			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
hypotension			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 18 (0.00%) 0	
General disorders and administration site conditions pyrexia alternative dictionary used: MedDRA 21.1 subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 18 (0.00%) 0	
Social circumstances menarche alternative dictionary used: MedDRA 21.1 subjects affected / exposed ^[1] occurrences (all)	0 / 10 (0.00%) 0	1 / 9 (11.11%) 1	
Reproductive system and breast disorders menorrhagia alternative dictionary used: MedDRA 21.1 subjects affected / exposed ^[2] occurrences (all) penis disorder alternative dictionary used: MedDRA 21.1 subjects affected / exposed ^[3] occurrences (all) spontaneous penile erection alternative dictionary used: MedDRA 21.1 subjects affected / exposed ^[4] occurrences (all)	1 / 10 (10.00%) 1 1 / 7 (14.29%) 1 1 / 7 (14.29%) 2	0 / 9 (0.00%) 0 0 / 9 (0.00%) 0 0 / 9 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders epistaxis alternative dictionary used: MedDRA 21.1 subjects affected / exposed occurrences (all) oropharyngeal pain alternative dictionary used: MedDRA 21.1 subjects affected / exposed occurrences (all)	2 / 17 (11.76%) 2 1 / 17 (5.88%) 1	1 / 18 (5.56%) 1 0 / 18 (0.00%) 0	

<p>pulmonary arterial hypertension</p> <p>alternative dictionary used: MedDRA 21.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 17 (0.00%)</p> <p>0</p>	<p>1 / 18 (5.56%)</p> <p>1</p>	
<p>Investigations</p> <p>hepatic enzyme increased</p> <p>alternative dictionary used: MedDRA 21.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 17 (5.88%)</p> <p>1</p>	<p>0 / 18 (0.00%)</p> <p>0</p>	
<p>Injury, poisoning and procedural complications</p> <p>bone contusion</p> <p>alternative dictionary used: MedDRA 21.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 17 (5.88%)</p> <p>1</p>	<p>0 / 18 (0.00%)</p> <p>0</p>	
<p>Cardiac disorders</p> <p>palpitations</p> <p>alternative dictionary used: MedDRA 21.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>tachycardia</p> <p>alternative dictionary used: MedDRA 21.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 17 (5.88%)</p> <p>1</p> <p>1 / 17 (5.88%)</p> <p>1</p>	<p>0 / 18 (0.00%)</p> <p>0</p> <p>0 / 18 (0.00%)</p> <p>0</p>	
<p>Nervous system disorders</p> <p>headache</p> <p>alternative dictionary used: MedDRA 21.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>presyncope</p> <p>alternative dictionary used: MedDRA 21.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>somnolence</p> <p>alternative dictionary used: MedDRA 21.1</p>	<p>5 / 17 (29.41%)</p> <p>5</p> <p>1 / 17 (5.88%)</p> <p>1</p>	<p>2 / 18 (11.11%)</p> <p>6</p> <p>0 / 18 (0.00%)</p> <p>0</p>	

subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 18 (0.00%) 0	
Blood and lymphatic system disorders eosinophilia alternative dictionary used: MedDRA 21.1 subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	1 / 18 (5.56%) 1	
Skin and subcutaneous tissue disorders haemorrhage subcutaneous alternative dictionary used: MedDRA 21.1 subjects affected / exposed occurrences (all) livedo reticularis alternative dictionary used: MedDRA 21.1 subjects affected / exposed occurrences (all) rash alternative dictionary used: MedDRA 21.1 subjects affected / exposed occurrences (all) swelling face alternative dictionary used: MedDRA 21.1 subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 3 0 / 17 (0.00%) 0 1 / 17 (5.88%) 1 1 / 17 (5.88%) 1	0 / 18 (0.00%) 0 1 / 18 (5.56%) 1 0 / 18 (0.00%) 0 0 / 18 (0.00%) 0	
Musculoskeletal and connective tissue disorders arthralgia alternative dictionary used: MedDRA 21.1 subjects affected / exposed occurrences (all) back pain alternative dictionary used: MedDRA 21.1 subjects affected / exposed occurrences (all)	2 / 17 (11.76%) 2 1 / 17 (5.88%) 1	1 / 18 (5.56%) 1 0 / 18 (0.00%) 0	
Infections and infestations			

bronchitis		
alternative dictionary used: MedDRA 21.1		
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	1
influenza		
alternative dictionary used: MedDRA 21.1		
subjects affected / exposed	3 / 17 (17.65%)	0 / 18 (0.00%)
occurrences (all)	3	0
pharyngitis		
alternative dictionary used: MedDRA 21.1		
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)
occurrences (all)	1	0
rhinitis		
alternative dictionary used: MedDRA 21.1		
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)
occurrences (all)	1	0
sinusitis		
alternative dictionary used: MedDRA 21.1		
subjects affected / exposed	1 / 17 (5.88%)	1 / 18 (5.56%)
occurrences (all)	1	1
upper respiratory tract infection		
alternative dictionary used: MedDRA 21.1		
subjects affected / exposed	3 / 17 (17.65%)	1 / 18 (5.56%)
occurrences (all)	3	1
urinary tract infection		
alternative dictionary used: MedDRA 21.1		
subjects affected / exposed	1 / 17 (5.88%)	1 / 18 (5.56%)
occurrences (all)	1	1
vaginal infection		
alternative dictionary used: MedDRA 21.1		
subjects affected / exposed ^[5]	1 / 10 (10.00%)	0 / 9 (0.00%)
occurrences (all)	1	0
viral tonsillitis		
alternative dictionary used: MedDRA 21.1		

subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
viral upper respiratory tract infection alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	
occurrences (all)	1	0	

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: This event is gender specific, only occurring in male or female subjects. The number of subjects exposed has been adjusted accordingly.

[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: This event is gender specific, only occurring in male or female subjects. The number of subjects exposed has been adjusted accordingly.

[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: This event is gender specific, only occurring in male or female subjects. The number of subjects exposed has been adjusted accordingly.

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Justification: This event is gender specific, only occurring in male or female subjects. The number of subjects exposed has been adjusted accordingly.

[5] - 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: This event is gender specific, only occurring in male or female subjects. The number of subjects exposed has been adjusted accordingly.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 September 2012	Change of primary endpoint for US from right heart catheterization (RHC) to Cardiac Echo. Per requirement from FDA that RHC can no longer be used as primary endpoint in Pediatric PAH trials.
14 December 2012	Per FDA removal of Tricuspid Annular Plane Systolic Excursion (TAPSE) as primary endpoint for US. Change of primary endpoint for US to improving time of 6-minute walk (6MW) test from baseline to week 24.
13 December 2018	Change of primary endpoint and study sample size.

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.

The study is mainly descriptive in a small number of children with PAH and there were no participants enrolled in the light weight cohort.

Notes: