



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 |
|-----------------------|-------------|

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 |
|------------------|-----------|

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) |
| 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 |
| 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 |
| 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 |
|----------------|-----------|

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 |
|-----------------|---|

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 |
|----------------|-----------|

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) | | |
|-------------------------------|--------------------|--------------------|--|--|

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 |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 21.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-----------|
| Reporting group title | Tadalafil |
|-----------------------|-----------|

Reporting group description:

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

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

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 | |

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

| | | | |
|---|--|--|--|
| 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.

[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: 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: