



Clinical trial results:

An open-label, long-term, safety, and tolerability extension study using the pediatric formulation of bosentan in the treatment of children with idiopathic or familial pulmonary arterial hypertension who completed FUTURE 1

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2005-001967-70 |
| Trial protocol | GB DE IT |
| Global end of trial date | 28 October 2011 |

Results information

| | |
|--------------------------------|----------------|
| Result version number | v2 (current) |
| This version publication date | 17 June 2016 |
| First version publication date | 06 August 2015 |
| Version creation reason | |

Trial information

Trial identification

| | |
|-----------------------|------------|
| Sponsor protocol code | AC-052-367 |
|-----------------------|------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00319020 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Actelion Pharmaceuticals Ltd |
| Sponsor organisation address | Gewerbestrasse 16, Allschwil, Switzerland, 4123 |
| Public contact | clinical trial disclosure desk, Actelion Pharmaceuticals Ltd, clinical-trials-disclosure@actelion.com |
| Scientific contact | clinical trial disclosure desk, Actelion Pharmaceuticals Ltd, clinical-trials-disclosure@actelion.com |

Notes:

Paediatric regulatory details

| | |
|--|-----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | Yes |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|-------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 25 September 2012 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 28 October 2011 |
| Global end of trial reached? | Yes |
| Global end of trial date | 28 October 2011 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To assess the long-term safety and tolerability of the pediatric formulation of bosentan in children with idiopathic or familial pulmonary arterial hypertension (iPAH or fPAH)

Protection of trial subjects:

This clinical study was designed and conducted in accordance with the ICH Harmonized Tripartite Guidelines for GCP, with applicable local regulations of the countries where the study was conducted, and with the ethical principles laid down in the Declaration of Helsinki.

Only patients who completed the FUTURE 1 study, who tolerated bosentan 32 mg dispersible tablets (pediatric formulation) during FUTURE 1 and for whom continuation of bosentan treatment was considered beneficial by the investigator, were offered the opportunity to participate in the FUTURE 1 Extension trial.

Background therapy:

The following concomitant medications were allowed at inclusion and during the study: calcium channel blockers, intravenous epoprostenol, intravenous or inhaled iloprost, anticoagulants, diuretics, digoxin

Evidence for comparator: -

| | |
|---|----------------|
| Actual start date of recruitment | 23 August 2005 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | France: 15 |
| Country: Number of subjects enrolled | Germany: 3 |
| Country: Number of subjects enrolled | Italy: 2 |
| Country: Number of subjects enrolled | Netherlands: 6 |
| Country: Number of subjects enrolled | Switzerland: 1 |
| Country: Number of subjects enrolled | United Kingdom: 2 |
| Country: Number of subjects enrolled | United States: 7 |
| Worldwide total number of subjects | 36 |
| EEA total number of subjects | 28 |

Notes:

Subjects enrolled per age group

| | |
|--|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 | 0 |

| | |
|--|----|
| wk | |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 36 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

36 Children (≥ 2 years and < 12 years) with idiopathic or familial pulmonary arterial hypertension were recruited from 11 centers across Europe and USA and enrolled in the FUTURE 1 trial (baseline). Only patients who completed FUTURE 1 ($n=34$) could be enrolled in FUTURE 2. Enrollment in FUTURE 2 started August 23, 2005.

Pre-assignment

Screening details:

The actual number of patients enrolled in FUTURE 2 was 33 because 2 patients did not complete FUTURE 1 and one patient completed FUTURE 1 but was not enrolled in FUTURE 2.

Period 1

| | |
|------------------------------|--|
| Period 1 title | Overall trial (FUTURE 1 + FUTURE 2) (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Blinding implementation details:

In this open-label extension trial, all subjects received the pediatric formulation of bosentan according to the core (FUTURE 1) study drug regimen, with the aim to determine its long term safety.

Arms

| | |
|------------------------------|---------------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Patients with previous bosentan |

Arm description:

This group included patients who already received bosentan (film-coated tablets) before enrollment in FUTURE 1, and then received the pediatric formulation of bosentan during FUTURE 1 and FUTURE 2 (see "Dosage and administration details" of the investigational medicinal compound).

Note: In this single arm trial, data are presented according to whether patients received bosentan or not before enrollment in FUTURE 1 but all the subjects received the study drug according to the same regimen.

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Bosentan |
| Investigational medicinal product code | ACT-050088 |
| Other name | |
| Pharmaceutical forms | Dispersible tablet |
| Routes of administration | Oral use |

Dosage and administration details:

The pediatric formulation of bosentan was initiated at a dose of 2 mg/kg b.i.d. for 4 weeks, then up-titrated to the maintenance dose of 4 mg/kg b.i.d. for the next 8 weeks of the FUTURE 1 trial (AC-052- 365) and to be continued in FUTURE 2. The dose could be down-titrated to 2 mg/kg b.i.d. if not tolerated. The body weight-adjusted dose of the dispersible tablet was dispersed in a teaspoon of water (not mixed with food) before being administered orally.

| | |
|------------------|-------------------------|
| Arm title | Bosentan-naive Patients |
|------------------|-------------------------|

Arm description:

This group included patients who were not treated with bosentan before enrollment in FUTURE 1, and received the pediatric formulation of bosentan during FUTURE 1 and FUTURE 2 (see "Dosage and administration details" of the investigational medicinal compound).

Note: In this single arm trial, data are presented according to whether patients received bosentan or not before enrollment in FUTURE 1 but all the subjects received the study drug according to the same regimen.

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
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| Number of subjects in period 1 | Patients with previous bosentan | Bosentan-naïve Patients |
|---|---------------------------------|-------------------------|
| Started | 15 | 21 |
| Enrollment in FUTURE 2 | 13 | 20 |
| Completed | 8 | 8 |
| Not completed | 7 | 13 |
| Consent withdrawn by subject | 4 | 1 |
| FUTURE 1 completed but not enrolled in FUTURE 2 | 1 | - |
| Disease progression | - | 2 |
| Treatment failure | - | 1 |
| Adverse event, non-fatal | - | 1 |
| Death | 2 | 2 |
| Transplant | - | 1 |
| Administrative reason | - | 5 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---------------------------------|
| Reporting group title | Patients with previous bosentan |
|-----------------------|---------------------------------|

Reporting group description:

This group included patients who already received bosentan (film-coated tablets) before enrollment in FUTURE 1, and then received the pediatric formulation of bosentan during FUTURE 1 and FUTURE 2 (see "Dosage and administration details" of the investigational medicinal compound).

Note: In this single arm trial, data are presented according to whether patients received bosentan or not before enrollment in FUTURE 1 but all the subjects received the study drug according to the same regimen.

| | |
|-----------------------|-------------------------|
| Reporting group title | Bosentan-naïve Patients |
|-----------------------|-------------------------|

Reporting group description:

This group included patients who were not treated with bosentan before enrollment in FUTURE 1, and received the pediatric formulation of bosentan during FUTURE 1 and FUTURE 2 (see "Dosage and administration details" of the investigational medicinal compound).

Note: In this single arm trial, data are presented according to whether patients received bosentan or not before enrollment in FUTURE 1 but all the subjects received the study drug according to the same regimen.

| Reporting group values | Patients with previous bosentan | Bosentan-naïve Patients | Total |
|---|---------------------------------|-------------------------|-------|
| Number of subjects | 15 | 21 | 36 |
| Age categorical | | | |
| Age when starting FUTURE 1 trial (baseline) | | | |
| Units: Subjects | | | |
| Children (2-3 years) | 1 | 3 | 4 |
| Children (4-5 years) | 3 | 6 | 9 |
| Children (6-11 years) | 11 | 12 | 23 |
| Age continuous | | | |
| Age when starting FUTURE 1 trial (baseline) | | | |
| Units: years | | | |
| median | 7 | 7 | |
| full range (min-max) | 3 to 10 | 2 to 11 | - |
| Gender categorical | | | |
| Units: | | | |
| Female | 5 | 10 | 15 |
| Male | 10 | 11 | 21 |
| Etiology of PAH | | | |
| Units: Subjects | | | |
| Idiopathic PAH | 12 | 19 | 31 |
| Familial PAH | 3 | 2 | 5 |
| Duration of PAH | | | |
| Units: months | | | |
| median | 37.6 | 14 | |
| full range (min-max) | 1.2 to 82.6 | 0 to 133.5 | - |

End points

End points reporting groups

| | |
|-----------------------|---------------------------------|
| Reporting group title | Patients with previous bosentan |
|-----------------------|---------------------------------|

Reporting group description:

This group included patients who already received bosentan (film-coated tablets) before enrollment in FUTURE 1, and then received the pediatric formulation of bosentan during FUTURE 1 and FUTURE 2 (see "Dosage and administration details" of the investigational medicinal compound).

Note: In this single arm trial, data are presented according to whether patients received bosentan or not before enrollment in FUTURE 1 but all the subjects received the study drug according to the same regimen.

| | |
|-----------------------|-------------------------|
| Reporting group title | Bosentan-naïve Patients |
|-----------------------|-------------------------|

Reporting group description:

This group included patients who were not treated with bosentan before enrollment in FUTURE 1, and received the pediatric formulation of bosentan during FUTURE 1 and FUTURE 2 (see "Dosage and administration details" of the investigational medicinal compound).

Note: In this single arm trial, data are presented according to whether patients received bosentan or not before enrollment in FUTURE 1 but all the subjects received the study drug according to the same regimen.

| | |
|----------------------------|-----------------|
| Subject analysis set title | All-treated set |
|----------------------------|-----------------|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Intention-to-treat |
|---------------------------|--------------------|

Subject analysis set description:

All patients (bosentan-naïve patients and patients treated with film-coated bosentan tablets before enrollment) who received at least one dose of study drug (dispersible bosentan tablets) in the combined FUTURE 1 / FUTURE 2 trial periods.

Primary: Change from baseline to end of study (EOS) in systolic blood pressure (SBP)

| | |
|-----------------|--|
| End point title | Change from baseline to end of study (EOS) in systolic blood pressure (SBP) ^[1] |
|-----------------|--|

End point description:

The main study objective was to assess the long-term safety of bosentan in children with PAH, including changes from baseline in blood pressure.

Only subjects with non missing data at both time points were considered.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From baseline (FUTURE 1) up to end of study or premature study treatment discontinuation (FUTURE 1 or FUTURE 2)

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: This was an exploratory study; no statistical hypothesis was set and only descriptive analyses were performed

| End point values | Patients with previous bosentan | Bosentan-naïve Patients | All-treated set | |
|---------------------------------|---------------------------------|-------------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 10 | 14 | 24 | |
| Units: mmHg | | | | |
| median (full range (min-max)) | | | | |
| SBP at baseline | 101.5 (87 to 115) | 104 (79 to 121) | 102.5 (79 to 121) | |
| SBP change from baseline to EOS | -10.5 (-20 to 25) | 4 (-21 to 28) | -4.5 (-21 to 28) | |

Statistical analyses

No statistical analyses for this end point

Primary: Change from baseline to end of study (EOS) in diastolic blood pressure (DBP)

| | |
|-----------------|---|
| End point title | Change from baseline to end of study (EOS) in diastolic blood pressure (DBP) ^[2] |
|-----------------|---|

End point description:

The main study objective was to assess the long-term safety of bosentan in children with PAH, including changes from baseline in blood pressure.

Only subjects with non missing data at both time points were considered.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From baseline (FUTURE 1) up to end of study or premature study treatment discontinuation (FUTURE 1 or FUTURE 2)

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: This was an exploratory study; no statistical hypothesis was set and only descriptive analyses were performed

| End point values | Patients with previous bosentan | Bosentan-naïve Patients | All-treated set | |
|---------------------------------|---------------------------------|-------------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 10 | 13 | 23 | |
| Units: mmHg | | | | |
| median (full range (min-max)) | | | | |
| DBP at baseline | 54.5 (47 to 94) | 60 (52 to 75) | 59 (47 to 94) | |
| DBP change from baseline to EOS | -5 (-34 to 19) | -2 (-13 to 20) | -3 (-34 to 20) | |

Statistical analyses

No statistical analyses for this end point

Primary: Change from baseline to end of study (EOS) in pulse rate

| | |
|-----------------|---|
| End point title | Change from baseline to end of study (EOS) in pulse rate ^[3] |
|-----------------|---|

End point description:

The main study objective was to assess the long-term safety of bosentan in children with PAH, including changes from baseline in pulse rate.

Only subjects with non missing data at both time points were considered.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From baseline (FUTURE 1) up to end of study or premature study treatment discontinuation (FUTURE 1 or FUTURE 2)

Notes:

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

Justification: This was an exploratory study; no statistical hypothesis was set and only descriptive analyses were performed

| End point values | Patients with previous bosentan | Bosentan-naïve Patients | All-treated set | |
|---|---------------------------------|-------------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 11 | 14 | 25 | |
| Units: beats per minutes | | | | |
| median (full range (min-max)) | | | | |
| Pulse rate at baseline | 87 (55 to 118) | 94.5 (62 to 133) | 88 (55 to 133) | |
| Pulse rate: change from baseline to EOS | -11 (-46 to 36) | -10 (-30 to 11) | -11 (-46 to 36) | |

Statistical analyses

No statistical analyses for this end point

Primary: Change from baseline to end of study (EOS) in body weight

| | |
|-----------------|--|
| End point title | Change from baseline to end of study (EOS) in body weight ^[4] |
|-----------------|--|

End point description:

The main study objective was to assess the long-term safety of bosentan in children with PAH, including growth as measured by changes from baseline in body weight and height.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From baseline (FUTURE 1) up to end of study or premature study treatment discontinuation (FUTURE 1 or FUTURE 2)

Notes:

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

Justification: This was an exploratory study; no statistical hypothesis was set and only descriptive analyses were performed

| End point values | Patients with previous bosentan | Bosentan-naïve Patients | All-treated set | |
|------------------------------------|---------------------------------|-------------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 10 | 14 | 24 | |
| Units: kg | | | | |
| median (full range (min-max)) | | | | |
| Weight at baseline | 19.6 (12.5 to 30.2) | 21.6 (11 to 39) | 19.6 (11 to 39) | |
| Weight change from baseline to EOS | 8.2 (5 to 24.8) | 8.5 (1.8 to 18.5) | 8.3 (1.8 to 24.8) | |

Statistical analyses

Primary: Change from baseline to end of study (EOS) in height for age

| | |
|-----------------|---|
| End point title | Change from baseline to end of study (EOS) in height for age ^[5] |
|-----------------|---|

End point description:

The main study objective was to assess the long-term safety of bosentan in children with PAH, including growth as measured by changes from baseline in body weight and height.

For each patient, height was put in the perspective of the height of healthy children of the same age according to the WHO growth standards.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From baseline (FUTURE 1) up to end of study or premature study treatment discontinuation (FUTURE 1 or FUTURE 2)

Notes:

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

Justification: This was an exploratory study; no statistical hypothesis was set and only descriptive analyses were performed

| End point values | Patients with previous bosentan | Bosentan-naïve Patients | All-treated set | |
|-------------------------------------|---------------------------------|-------------------------|-----------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 10 | 14 | 24 | |
| Units: Z-score | | | | |
| median (full range (min-max)) | | | | |
| Z-score at baseline | -0.8 (-3.32 to 3.72) | 0.32 (-2.62 to 1.99) | -0.64 (-3.32 to 3.72) | |
| Z-score at EOS | -0.74 (-3.52 to 2.78) | -0.08 (-2.44 to 1.84) | -0.36 (-3.52 to 2.78) | |
| Z-score change from baseline to EOS | -0.05 (-0.94 to 0.91) | -0.01 (-0.77 to 1.08) | -0.01 (-0.94 to 1.08) | |

Statistical analyses

No statistical analyses for this end point

Primary: Proportion of patients with treatment-emergent liver function abnormalities

| | |
|-----------------|--|
| End point title | Proportion of patients with treatment-emergent liver function abnormalities ^[6] |
|-----------------|--|

End point description:

The main study objective was to assess the long-term safety of bosentan in children with PAH, including laboratory abnormalities related to liver enzymes.

Proportion of patients with increase in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) above 3 x ULN (upper limit of normal) is reported here.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

After baseline, up to 1 calendar day after study drug discontinuation in FUTURE 1 or FUTURE 2

Notes:

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

Justification: This was an exploratory study; no statistical hypothesis was set and only descriptive analyses were performed

| End point values | Patients with previous bosentan | Bosentan-naive Patients | All-treated set | |
|-----------------------------|---------------------------------|-------------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 15 | 21 | 36 | |
| Units: Percentage | | | | |
| number (not applicable) | | | | |
| ALT > 3x ULN | 0 | 4.8 | 2.8 | |
| AST > 3 x ULN | 0 | 4.8 | 2.8 | |

Statistical analyses

No statistical analyses for this end point

Primary: Proportion of patients with treatment-emergent hemoglobin abnormalities

| | |
|-----------------|--|
| End point title | Proportion of patients with treatment-emergent hemoglobin abnormalities ^[7] |
|-----------------|--|

End point description:

The main study objective was to assess the long-term safety of bosentan in children with PAH, including hemoglobin abnormalities.

Proportion of patients with marked hemoglobin decreases (i.e., decrease of or above 15% of the lower normal limit (LL)) is reported here.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

After baseline, up to 1 calendar day after study drug discontinuation in FUTURE 1 or FUTURE 2

Notes:

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

Justification: This was an exploratory study; no statistical hypothesis was set and only descriptive analyses were performed

| End point values | Patients with previous bosentan | Bosentan-naive Patients | All-treated set | |
|-----------------------------|---------------------------------|-------------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 15 | 21 | 36 | |
| Units: percentage | | | | |
| number (not applicable) | 13.3 | 9.5 | 11.1 | |

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with adverse events leading to premature discontinuation of study treatment

| | |
|-----------------|---|
| End point title | Number of subjects with adverse events leading to premature discontinuation of study treatment ^[8] |
|-----------------|---|

End point description:

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From the first study drug administration in FUTURE 1

Notes:

[8] - 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: This was an exploratory study; no statistical hypothesis was set and only descriptive analyses were performed

| End point values | Patients with previous bosentan | Bosentan-naïve Patients | All-treated set | |
|-----------------------------|---------------------------------|-------------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 15 | 21 | 36 | |
| Units: Number of subjects | 1 | 5 | 6 | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From study drug initiation up to 1 day after study drug discontinuation (up to 28 days after study drug discontinuation for serious adverse events)

Adverse event reporting additional description:

Four deaths occurred during this time frame and two other deaths (1 due to PAH and cardiac complications and 1 during cardiac catheterization; not listed below) occurred later (38 days and 11 months after study drug discontinuation, respectively).

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 14.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-----------------|
| Reporting group title | All treated set |
|-----------------------|-----------------|

Reporting group description:

The 36 patients included in this analysis set were exposed to the study drug (pediatric formulation of bosentan), for at least 8.4 weeks up to a maximum of 258 weeks (median: 119.9 weeks).

| Serious adverse events | All treated set | | |
|---|------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 18 / 36 (50.00%) | | |
| number of deaths (all causes) | 6 | | |
| number of deaths resulting from adverse events | 0 | | |
| Investigations | | | |
| Arterial catheterisation | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Catheterisation cardiac | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary arterial pressure | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 36 (2.78%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Right ventricular failure | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 2 | | |
| Cardiac failure | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Pericardial effusion | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Surgical and medical procedures | | | |
| Systemic pulmonary artery shunt | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Adenoidectomy | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Balloon atrial septostomy | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|--|----------------|--|--|
| Nervous system disorders | | | |
| Convulsion | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dystonia | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Syncope | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Iron deficiency anaemia | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Chest pain | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injection site nodule | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Medical device complication | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 36 (2.78%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pulmonary arterial hypertension | | | |
| subjects affected / exposed | 3 / 36 (8.33%) | | |
| occurrences causally related to treatment / all | 1 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary hypertension | | | |
| subjects affected / exposed | 3 / 36 (8.33%) | | |
| occurrences causally related to treatment / all | 1 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bronchial obstruction | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cough | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diaphragmatic hernia | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary vein stenosis | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|----------------|--|--|
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Wheezing | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| Autoimmune hepatitis | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Flank pain | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Device related infection | | | |
| subjects affected / exposed | 3 / 36 (8.33%) | | |
| occurrences causally related to treatment / all | 0 / 7 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bacteraemia | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bronchitis viral | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Catheter site infection | | | |

| | | | | |
|---|----------------|--|--|--|
| subjects affected / exposed | 1 / 36 (2.78%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cellulitis | | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Ear infection | | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lobar pneumonia | | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lung infection | | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumonia | | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumonia viral | | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Viral infection | | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Viral rhinitis | | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 36 (2.78%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | All treated set | | |
|---|------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 26 / 36 (72.22%) | | |
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | | |
| occurrences (all) | 2 | | |
| Vascular disorders | | | |
| Flushing | | | |
| subjects affected / exposed | 4 / 36 (11.11%) | | |
| occurrences (all) | 5 | | |
| Cardiac disorders | | | |
| Cyanosis | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | | |
| occurrences (all) | 2 | | |
| Palpitations | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | | |
| occurrences (all) | 4 | | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 4 / 36 (11.11%) | | |
| occurrences (all) | 7 | | |
| Dizziness | | | |
| subjects affected / exposed | 3 / 36 (8.33%) | | |
| occurrences (all) | 4 | | |
| Syncope | | | |
| subjects affected / exposed | 3 / 36 (8.33%) | | |
| occurrences (all) | 6 | | |
| General disorders and administration site conditions | | | |

| | | | |
|-----------------------------|-----------------|--|--|
| Asthenia | | | |
| subjects affected / exposed | 3 / 36 (8.33%) | | |
| occurrences (all) | 4 | | |
| Chest pain | | | |
| subjects affected / exposed | 3 / 36 (8.33%) | | |
| occurrences (all) | 10 | | |
| Pyrexia | | | |
| subjects affected / exposed | 3 / 36 (8.33%) | | |
| occurrences (all) | 3 | | |
| Adverse drug reaction | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | | |
| occurrences (all) | 3 | | |
| Fatigue | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | | |
| occurrences (all) | 3 | | |
| Ear and labyrinth disorders | | | |
| Ear pain | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | | |
| occurrences (all) | 3 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 6 / 36 (16.67%) | | |
| occurrences (all) | 7 | | |
| Vomiting | | | |
| subjects affected / exposed | 4 / 36 (11.11%) | | |
| occurrences (all) | 4 | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 3 / 36 (8.33%) | | |
| occurrences (all) | 4 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 3 / 36 (8.33%) | | |
| occurrences (all) | 3 | | |
| Constipation | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | | |
| occurrences (all) | 2 | | |
| Nausea | | | |

| | | | |
|---|-----------------------|--|--|
| subjects affected / exposed occurrences (all) | 2 / 36 (5.56%) 2 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pulmonary arterial hypertension subjects affected / exposed occurrences (all) | 4 / 36 (11.11%) 4 | | |
| Nasal congestion subjects affected / exposed occurrences (all) | 3 / 36 (8.33%) 4 | | |
| Pulmonary hypertension subjects affected / exposed occurrences (all) | 3 / 36 (8.33%) 3 | | |
| Cough subjects affected / exposed occurrences (all) | 2 / 36 (5.56%) 4 | | |
| Epistaxis subjects affected / exposed occurrences (all) | 2 / 36 (5.56%) 2 | | |
| Psychiatric disorders | | | |
| Aggression subjects affected / exposed occurrences (all) | 2 / 36 (5.56%) 2 | | |
| Renal and urinary disorders | | | |
| Enuresis subjects affected / exposed occurrences (all) | 2 / 36 (5.56%) 2 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Pain in extremity subjects affected / exposed occurrences (all) | 2 / 36 (5.56%) 2 | | |
| Infections and infestations | | | |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 7 / 36 (19.44%) 11 | | |
| Bronchitis | | | |

| | | | |
|-----------------------------------|-----------------|--|--|
| subjects affected / exposed | 5 / 36 (13.89%) | | |
| occurrences (all) | 6 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 5 / 36 (13.89%) | | |
| occurrences (all) | 7 | | |
| Pneumonia | | | |
| subjects affected / exposed | 3 / 36 (8.33%) | | |
| occurrences (all) | 7 | | |
| H1N1 influenza | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | | |
| occurrences (all) | 2 | | |
| Influenza | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | | |
| occurrences (all) | 2 | | |
| Otitis media | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | | |
| occurrences (all) | 2 | | |
| Pharyngitis | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | | |
| occurrences (all) | 2 | | |
| Tonsilitis | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | | |
| occurrences (all) | 3 | | |
| Viral infection | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | | |
| occurrences (all) | 2 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|----------------|--|
| 27 August 2008 | The purpose of this amendment is to adjust the monitoring schedule during this open label extension study. |

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.

In 3 patients new therapy was initiated in spite of absence of clinical worsening, reflecting a changing treatment paradigm towards combination therapy. The patients were kept in the time to PAH worsening analyses.

Notes: