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 oppurtunity 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 uptitrated 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.

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Number of subjects in period 1	Patients with previous bosentan	Bosentan-naive 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-naive 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-naive 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-naive 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-naive 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-naive 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-naive 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-naive 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-naive 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

No statistical analyses for this end point

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

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